(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 May 2001 (03.05.2001)

PCT

(10) International Publication Number
WO 01/30745 A1

(51) International Patent Classification[7]: C07C 237/30, 327/32, 255/58, A61K 31/166, 31/40, 31/277, 31/357, A61P 9/10, C07C 255/59, 271/20, C07D 207/14, 317/72

(21) International Application Number: PCT/JP00/07308

(22) International Filing Date: 19 October 2000 (19.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PQ 3652 25 October 1999 (25.10.1999) AU

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

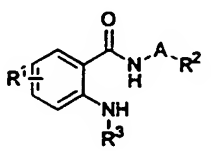
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/30745 A1

(54) Title: ANTHRANILIC ACID DERIVATIVES AS INHIBITORS OF THE CGMP-PHOSPHODIESTERASE



(I)

(57) Abstract: This invention relates to a compound of formula (I): wherein R^1 is nitro group, amino group, cyano group, a halo(lower)alkyl group, a halogen atom, etc., R^2 is an optionally substituted aryl group, A is a lower alkylene group, and R^3 is an optionally substituted heterocyclic group, or a group of formula: $-CR^4R^5R^6$, in which R^4 and R^5 are each independently an optionally substituted carbamoyl group or an optionally substituted lower alkyl group, or R^4 and R^5 together with the carbon atom to which R^4 and R^5 are attached may form an optionally substituted carbocyclic group, and R^6 is hydrogen atom or a lower alkyl group, etc., and a prodrug and a acceptable salt thereof, to processes for preparation thereof, to a pharmaceutical composition containing the same, and to a method for the prevention and/or the treatment of various diseases, such as erectile dysfunction.

DESCRIPTION

ANTHRANILIC ACID DERIVATIVES AS INHIBITORS OF THE CGMP-PHOSPHODIESTERASE

TECHNICAL FIELD

This invention relates to novel anthranilic acid derivatives having pharmacological activity, to a process for their production, to a pharmaceutical composition containing the same, and to their use as a medicament.

BACKGROUND ART

It is known that a cyclic guanosine-3',5'-monophosphate (hereinafter referred to as cGMP) derived from a guanosine-5'-triphosphate possesses a relaxant activity of smooth muscle and that a cyclic guanosine-3',5'-monophosphate phosphodiesterase (hereinafter referred to as cGMP-PDE) acts to catalyze the degradation of cGMP to a guanosine-5'-monophosphate. The compounds having an inhibitory activity of cGMP-PDE are disclosed in European Patent Publication Nos. 579,496; 534,443; 526,004; 636,626; United States Patent Nos. 3,819,631; 5,294,612; 5,488,055; International Patent Publication Nos. 93/07,124; 94/19,351; 95/18,097; 96/32,379; Japan Patent Publication Nos. 05-222,000; 07-330,777; and so on.

DISCLOSURE OF INVENTION

This invention relates to novel anthranilic acid derivatives, which have pharmacological activity such as inhibiting activity of cGMP-PDE, to a process for their production, to a pharmaceutical composition containing the same and to a use thereof.

Accordingly, an object of this invention is to provide the novel anthranilic acid derivatives, which have an inhibitory activity of cGMP-PDE.

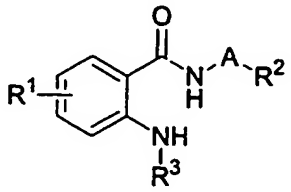
Another object of this invention is to provide a process for production of the anthranilic acid derivatives.

A further object of this invention is to provide a pharmaceutical composition containing, as an active ingredient, the anthranilic acid

derivatives.

Still further object of this invention is to provide a use of the anthranilic acid derivatives for treating or preventing various diseases.

The new anthranilic acid derivatives of this invention are represented by the following formula [I] :



[I]

wherein

R^1 is nitro group, amino group, cyano group, an acyl group, a halo(lower)alkyl group, sulfamoyl group, a carbamoyl group optionally substituted with lower alkyl, a halogen atom, a lower alkenyl group optionally substituted with protected carboxy, a lower alkanesulfonyl group, a saturated heterocyclic sulfonyl group optionally substituted with protected carboxy or an unsaturated heterocyclic group,

R^2 is hydrogen atom, hydroxy group, a lower alkoxy group, a lower alkyl group, a cycloalkyl group, an optionally substituted aryl group or a heterocyclic group optionally substituted with lower alkyl,

A is a lower alkylene group and

R^3 is an optionally substituted heterocyclic group or a group of the formula : $-CR^4R^5R^6$, in which

R^4 and R^5 are each independently

a carbamoyl group or a lower alkyl group optionally substituted with one or more substituent(s) selected from the group consisting of hydroxy group and an amino group optionally substituted with acyl, protected carboxy, carbamoyl or lower alkylcarbamoyl, or

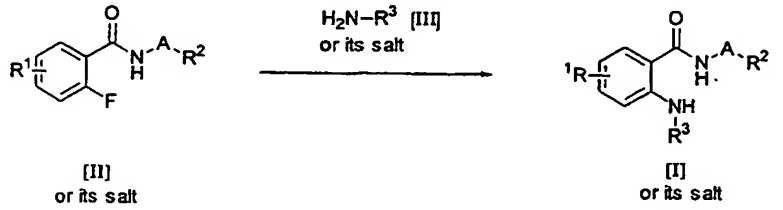
R^4 and R^5 together with the carbon atom to which R^4 and R^5

are attached may form an optionally substituted carbocyclic group, and

R^6 is hydrogen atom or a lower alkyl group.

According to this invention, the object compounds [I] or their salts can be prepared by the following processes:

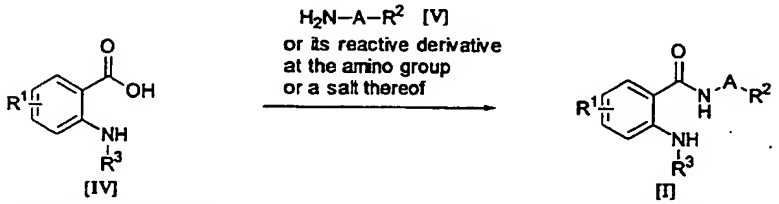
Process 1



[II]
or its salt

[I]
or its salt

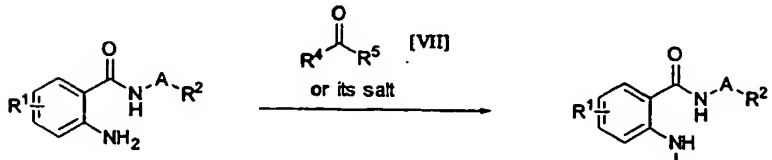
Process 2



[IV]
or its reactive derivative
at the carboxy group
or a salt thereof

[I]
or its salt

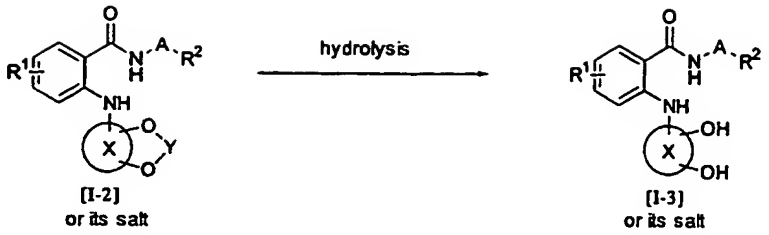
Process 3



[VI]
or its salt

[I-1]
or its salt

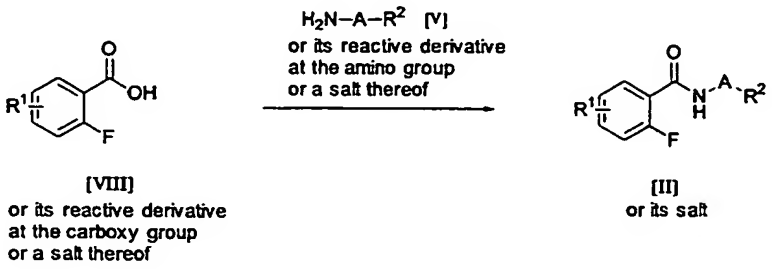
Process 4



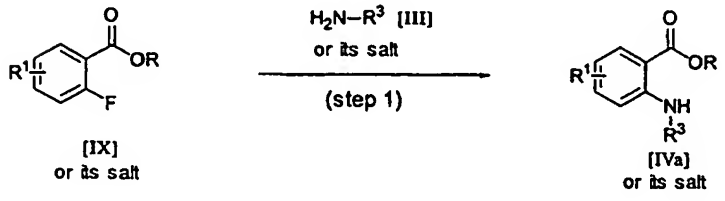
wherein a ring (X) is a carbocyclic group,
Y is cycloalkylidene, and
R^1, R^2, R^3, R^4, R^5 and A are the same as those defined in the above.

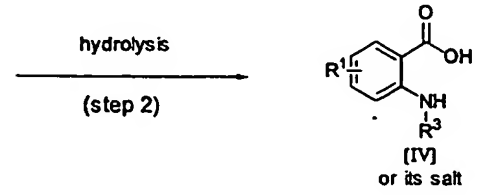
Some of the starting materials are novel and can be prepared by the following processes:

Process A

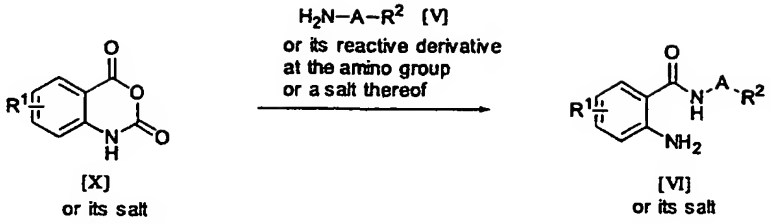


Process B





Process C



wherein R is lower alkyl, and R^1, R^2, R^3 and A are the same as those defined in the above.

In the above and subsequent descriptions of the present specification and claims, suitable examples and illustrations of the various definitions which the present invention includes within the scope are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise indicated.

Suitable lower alkyl groups and lower alkyl moieties in the terms of the lower alkanesulfonyl, lower alkylcarbamoyl, lower alkoxy, lower alkylthio and hydroxy(lower)alkyl groups may include straight or branched ones having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, isopentyl, hexyl or the like, more suitably the ones having 1 to 4 carbon atom(s) such as methyl, ethyl, propyl, isopropyl, butyl or isobutyl.

Suitable lower alkenyl groups may include straight or branched ones having 2 to 6 carbon atoms, such as ethenyl, propenyl [i.e., allyl or 1-propenyl], butenyl, isobutenyl, pentenyl, hexenyl or the like.

Suitable lower alkylene groups and lower alkylene moieties in the terms of the lower alkylenedioxy groups may include straight or branched ones having 1 to 6 carbon atom(s), such as methylene, methylmethylene, ethylene, methylethylene, trimethylene, tetramethylene, 2-methyltrimethylene, pentamethylene, hexamethylene or the like, more suitably the ones having 1 to 3 carbon atom(s).

Suitable acyl groups and acyl moieties in the terms f the acyloxy groups may include aliphatic acyl groups such as lower alkanoyl groups [e.g., formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl or pivaloyl] and acyl groups containing an aromatic or heterocyclic ring such as aroyl groups [e.g., benzoyl, toluoyl, xyloyl or naphthoyl], ar(lower)alkanoyl groups [e.g., phenylacetyl or phenylpropionyl], ar(lower)alkoxycarbonyl groups [e.g., benzyloxycarbonyl or phenethyloxycarbonyl], heterocyclic carbonyl groups [e.g., thenoyl or furoyl] and the like.

Suitable cycloalkyl groups and cycloalkyl moieties in the terms of the cycloalkylidene and cycloalkylidenedioxy groups may include the ones having 3 to 7 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or the like.

Suitable aryl groups and aryl moieties in the terms of the aryloxy groups may be phenyl, naphthyl, indenyl, azulenyl, biphenylenyl, fluorenyl, anthracenyl or the like, in which more preferable ones are phenyl or naphthyl.

The carbocyclic groups includes saturated and unsaturated carbocyclic groups.

Suitable saturated carbocyclic groups are the cycloalkyl groups as exemplified in the above.

Suitable unsaturated carbocyclic groups may include cycloalkenyl groups [e.g., cyclopentenyl, cyclohexenyl or cycloheptenyl], 2,3-dihydro-1H-indenyl, benzocyclohexyl and the like.

Suitable halogen atoms and halo moieties of halo(lower)alkyl groups may be fluorine, chlorine, bromine or iodine.

The heterocyclic groups include saturated and unsaturated heterocyclic groups.

Suitable unsaturated heterocyclic groups may include mono- or poly-cyclic groups containing at least one hetero atom selected from nitrogen, sulfur and oxygen atoms, such as

(1) unsaturated 3 to 7-membered, preferably 5 or 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl,

pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl or 2H-1,2,3-triazolyl] or tetrazolyl [e.g., 1H-tetrazoly or 2H-tetrazolyl];

(2) unsaturated 3 to 7-membered, preferably 5 or 6-membered heteromonocyclic groups containing an oxygen atom, for example, pyranyl or furyl;

(3) unsaturated 3 to 7-membered, preferably 5 or 6-membered heteromonocyclic groups containing 1 to 2 sulfur atom(s), for example, thienyl;

(4) unsaturated 3 to 7-membered, preferably 5 or 6-membered heteromonocyclic groups containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl or oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl or 1,2,5-oxadiazolyl];

(5) unsaturated 3 to 7-membered, preferably 5 or 6-membered heteromonocyclic groups containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl or thiadiazolyl [e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl or 1,2,5-thiadiazolyl];

(6) unsaturated condensed heterocyclic groups containing 1 to 2 nitrogen atom(s), for example, indolyl, indazolyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl or benzimidazolyl;

(7) unsaturated condensed heterocyclic groups containing 1 to 2 oxygen atom(s), for example, benzofuryl;

(8) unsaturated condensed heterocyclic groups containing 1 to 2 sulfur atom(s), for example, benzo[b]thienyl;

(9) unsaturated condensed heterocyclic groups containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl or phenoxazinyl; and

(10) unsaturated condensed heterocyclic groups containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzoisothiazolyl or phenothiazinyl.

Suitable saturated heterocyclic groups may include monocyclic groups containing at least one hetero atom selected from nitrogen, sulfur and oxygen atoms, such as

(1) saturated 3 to 7-membered, preferably 5 or 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atom(s) [e.g., pyrrolidinyl, imidazolidinyl, piperidyl or piperazinyl];

(2) saturated 3 to 7-membered, preferably 5 or 6-membered heteromonocyclic groups containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) [e.g., morpholinyl];
(3) saturated 3 to 7-membered, preferably 5 or 6-membered heteromonocyclic groups containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) [e.g., thiazolidinyl or thiomorpholinyl];
(4) saturated 3 to 7-membered, preferably 5 or 6-membered heteromonocyclic groups containing 1 to 2 sulfur atoms and/or 1 to 2 oxygen atom(s) [e.g., tetrahydrothenyl, tetrahydrothiopyranyl, 1-oxotetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl, dioxacyclohexyl, tetrahydrofuranyl, tetrahydropyranyl or dioxanyl]; and the like.

Suitable substituents on the aryl groups in the terms of the optionally substituted aryl groups may be a lower alkyl group, a halo(lower)alkyl group, a lower alkylthio group, a halogen atom, hydroxy group, a lower alkylenedioxy group, cyano group, nitro group, carboxy group, a protected carboxy group, sulfamoyl group, an acyl group, an aryl group, an ar(lower)alkoxy group (e.g., benzyloxy, 4-methoxybenzyloxy, 4-nitrobenzyloxy, phenethyloxy, trityloxy, bis(methoxyphenyl)methoxy, 3,4-dimethoxybenzyloxy or 4-hydroxy-3,5-di-*tert*-butylbenzyloxy), an aryloxy group, a lower alkoxy group optionally substituted with lower alkoxy or cycloalkyl, an amino group optionally substituted with acyl, protected carboxy or lower alkyl, or a carbamoyl group optionally substituted with lower alkyl.

Suitable substituents on the heterocyclic groups in the terms of optionally substituted heterocyclic groups may be oxo group, an acyl group, a protected carboxy group, a lower alkanesulfonyl group, a sulfamoyl group optionally substituted with protected carboxy, an ar(lower)alkyl group [e.g., benzyl, 4-methoxybenzyl, 4-nitrobenzyl, phenethyl, trityl, bis(methoxyphenyl)methyl, 3,4-dimethoxybenzyl or 4-hydroxy-3,5-di-*tert*-butylbenzyl], a lower alkyl group optionally substituted with hydroxy or aryl, an ureido group optionally substituted with lower alkyl, a guanidino group optionally substituted with protected carboxy, an amidino group optionally substituted with protected

carboxyl, or a carbamoyl group optionally substituted with lower alkyl.

Suitable substituents on the carbocyclic groups in the terms of optionally substituted carbocyclic groups may be a lower alkyl, a halogen atom, hydroxy group, a lower alkoxy group, a protected hydroxy group, carboxy group, a protected carboxy group, oxo group, an amidino group optionally substituted with protected carboxy, an ureido group optionally substituted with lower alkyl or aryl, a guanidino group optionally substituted with protected carboxy, an amino group optionally substituted with acyl, lower alkanesulfonyl or protected carboxy, a carbamoyl group optionally substituted with lower alkyl, a hydroxy(lower)alkyl group, a lower alkylenedioxy group optionally substituted with oxo or a cycloalkylidenedioxy group.

Suitable protected carboxy groups may include lower alkoxycarbonyl groups [e.g., methoxycarbonyl, ethoxycarbonyl or *tert*-butoxycarbonyl], halo(lower)alkoxycarbonyl groups [e.g., 2-iodomethoxycarbonyl or 2,2,2-trichloroethoxycarbonyl], optionally substituted ar(lower)alkoxycarbonyl groups [e.g., benzyloxycarbonyl, trityloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, phenethyloxycarbonyl, bis(methoxyphenyl)methoxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl or 4-hydroxy-3,5-di-*tert*-butylbenzyloxycarbonyl], aryloxycarbonyl groups [e.g., phenyloxycarbonyl, naphthyloxycarbonyl, tolyloxycarbonyl or xylyloxycarbonyl], and the like, more suitably lower alkoxycarbonyl groups such as methoxycarbonyl, ethoxycarbonyl or *tert*-butoxycarbonyl, and ar(lower)alkoxycarbonyl groups such as benzyloxycarbonyl.

Suitable protected hydroxy groups may include acyloxy groups, cyclo(lower)alkenyloxy groups [preferable examples are cyclo C_3-C_6 alkenyloxy groups such as cyclopentenyloxy or cyclohexenyloxy], ar(lower)alkoxy groups optionally substituted with one or more suitable substituent(s), trisubstituted silyloxy groups [e.g., trimethylsilyloxy or *tert*-butyldimethylsilyloxy], tetrahydropyranyloxy groups and the like.

Suitable halo(lower)alkyl groups may be fluoromethyl, iodomethyl, chloromethyl, trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl or the like.

Among the above, the carbamoyl group for R^1 may be substituted with lower alkyl, the lower alkenyl group for R^1 may be substituted with protected carboxy, the saturated heterocyclic sulfonyl group for R^1 may be substituted with protected carboxy and the heterocyclic group for R^2 may be substituted with lower alkyl.

Suitable pharmaceutically acceptable salts of the object compounds [I] are conventional non-toxic salts and include a salt with an alkali metal [e.g., sodium or potassium] and an alkaline earth metal [e.g., calcium or magnesium], an ammonia, an organic base [e.g., trimethylamine, triethylamine, pyridine, picoline, dicyclohexylamine or N,N'-dibenzylethylenediamine], an organic acid [e.g., formic acid, acetic acid, trifluoroacetic acid, maleic acid, tartaric acid, oxalic acid, methanesulfonic acid, benzenesulfonic acid or toluenesulfonic acid], an inorganic acid [e.g., hydrogen chloride, hydrogen bromide, sulfuric acid or phosphoric acid], an amino acid [e.g., arginine, aspartic acid or glutamic acid] or the like.

With respect to the salts of the compounds [I-1] to [I-3] in the Processes 3 or 4, it is to be noted that these compounds are included within the scope of the compound [I], and accordingly the suitable examples of the salts of these compounds are to be referred to those as exemplified for the object compound [I].

Preferred embodiments of the object compounds [I] are those of the formula [I] wherein:

R^1 is nitro group, amino group, cyano group, an acyl group, a halo(lower)alkyl group, sulfamoyl group, a carbamoyl group optionally substituted with lower alkyl, a halogen atom, a lower alkenyl group optionally substituted with protected carboxy, a lower alkanesulfonyl group, a saturated heterocyclic sulfonyl group optionally substituted with protected carboxy, or an unsaturated heterocyclic group which is 3 to 7-membered, preferably 5 or 6-membered heterocyclic group containing 1 to 4 nitrogen atoms,

preferably, nitro group, amino group, cyano group, a

halo(lower)alkyl group or a halogen atom;

R^2 is hydrogen atom, hydroxy group, a lower alkoxy group, a lower alkyl group, a cycloalkyl group,

an aryl group optionally substituted with one or more substituent(s) selected from the group consisting of a lower alkyl group, a halo(lower)alkyl group, a lower alkylthio group, a halogen atom, hydroxy group, a lower alkylenedioxy group, cyano group, nitro group, carboxy group, protected carboxy group, sulfamoyl group, an acyl group, an aryl group, an ar(lower)alkoxy group, an aryloxy group, a lower alkoxy group optionally substituted with lower alkoxy or cycloalkyl, an amino group optionally substituted with acyl, protected carboxy or lower alkyl, and a carbamoyl group optionally substituted with lower alkyl, or

a 3 to 7-membered, preferably 5 or 6-membered heterocyclic group containing 1 to 4 nitrogen atom(s) optionally substituted with lower alkyl,

preferably, hydrogen atom, a lower alkyl group, a cycloalkyl group, a phenyl group or a naphthyl group, each of which may be substituted with one or more substituent(s) selected from the group consisting of a halogen atom, cyano group, a lower alkyl group and a lower alkoxy group, or pyridyl group,

A is a lower alkylene group, preferably, methylene,

and

R^3 is a saturated 3 to 7-membered, preferably 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) or 1 to 2 oxygen atom(s) optionally substituted with one or more substituent(s) selected from the group consisting of oxo group, an acyl group, a protected carboxy group, a lower alkanesulfonyl group, a sulfamoyl group optionally substituted with protected carboxy, an ar(lower)alkyl group, a lower alkyl group optionally substituted with hydroxy or aryl, an ureido group optionally substituted with lower alkyl, a guanidino group optionally substituted with protected carboxy, an amidino group optionally substituted with protected carboxy and a carbamoyl group optionally substituted with lower alkyl,

preferably, a saturated 3 to 7-membered, preferably 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) or 1 to 2 oxygen atom(s) optionally substituted with one or more substituent(s) selected from the group consisting of carbamoyl group, sulfamoyl group, a protected carboxy group and a lower alkyl group optionally substituted with hydroxy,
more preferably, a pyrrolidinyl group or a dioxanyl group, each of which may be substituted with one or more substituent(s) selected from the group consisting of carbamoyl group, sulfamoyl group, a lower alkoxycarbonyl group and a lower alkyl group optionally substituted with hydroxy or
a group of the formula : $-CR^4R^5R^6$ in which
R^4 and R^5 are each independently
a carbamoyl group or a lower alkyl group optionally substituted with one or more substituent(s) selected from the group consisting of hydroxy group and an amino group optionally substituted with acyl, protected carboxy, carbamoyl or lower alkylcarbamoyl or
R^4 and R^5 together with the carbon atom to which R^4 and R^5 are attached may form a carbocyclic group optionally substituted with one or more substituent(s) selected from the group consisting of a lower alkyl group, a halogen atom, hydroxy group, a lower alkoxy group, a protected hydroxy group, carboxy group, a protected carboxy group, oxo group, an amidino group optionally substituted with protected carboxy, an ureido group optionally substituted with lower alkyl or aryl, a guanidino group optionally substituted with protected carboxy, an amino group optionally substituted with acyl, lower alkanesulfonyl or protected carboxy, a carbamoyl group optionally substituted with lower alkyl, a hydroxy(lower)alkyl group, a lower alkylenedioxy group optionally substituted with oxo, and a cycloalkylidenedioxy group,
more preferably, R^4 and R^5 are each independently

a carbamoyl group or a lower alkyl group optionally substituted with one or more substituent(s) selected from the group consisting of hydroxy group and an amino group optionally substituted with lower alkanoyl, lower alkoxycarbonyl or lower alkylcarbamoyl, or

R^4 and R^5 together with the carbon atom to which R^4 and R^5 are attached may form a cycloalkyl group or a cycloalkenyl group, each of which may be substituted with one or more substituent(s) selected from the group consisting of a lower alkyl group, hydroxy group, a protected hydroxy group, a lower alkoxy group, an amino group optionally substituted with lower alkanoyl, an ureido group optionally substituted with lower alkyl, a lower alkylenedioxy group optionally substituted with oxo, and a cycloalkylidenedioxy group, and

R^6 is hydrogen atom or a lower alkyl group,

and their pro-drugs thereof, and salts thereof.

Further preferred embodiments are those of the formula [I] wherein :

R^1 is nitro group, amino group, cyano group, a halo(lower)alkyl group or a halogen atom,

R^2 is hydrogen atom, a lower alkyl group, a cycloalkyl group, an aryl group optionally substituted with one or more substituent(s) selected from the group consisting of a halogen atom, cyano group, a lower alkyl group and a lower alkoxy group, or pyridyl group,

A is a lower alkylene group and

R^3 is a saturated 3 to 7-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) or 1 to 2 oxygen atom(s) optionally substituted with one or more substituent(s) selected from the group consisting of carbamoyl group, sulfamoyl group, a protected carboxy group and a lower alkyl group optionally substituted with hydroxy, or

a group of the formula : $-CR^4R^5R^6$, in which

R^4 and R^5 are each independently a carbamoyl group or a lower alkyl group optionally substituted with one or more substituent(s) selected from the group consisting of hydroxy group and an amino group optionally substituted with acyl, protected carboxy, carbamoyl or lower alkylcarbamoyl, or

R^4 and R^5 together with the carbon atom to which R^4 and R^5 are attached may form a carbocyclic group optionally substituted with one or more substituent(s) selected from the group consisting of a lower alkyl group, hydroxy group, a protected hydroxy group, a lower alkoxy group, an amino group optionally substituted with acyl, an ureido group optionally substituted with lower alkyl, a lower alkylenedioxy group optionally substituted with oxo and a cycloalkylidenedioxy group, and

R^6 is hydrogen atom or a lower alkyl group,

and their prodrugs, and salts thereof.

Still further preferred embodiments of the compounds [I] are those of the formula [I] wherein:

R^1 is nitro group, amino group, cyano group, a halo(lower)alkyl group or a halogen atom,

R^2 is hydrogen atom, a lower alkyl group, a cycloalkyl group, an aryl group optionally substituted with one or more substituent(s) selected from the group consisting of a halogen atom, cyano group, a lower alkyl group and a lower alkoxy group, or pyridyl group,

A is a lower alkylene group,

and

R^3 is a group of the formula : $-CR^4R^5R^6$ in which

R^4 and R^5 together with the carbon atom to which R^4 and R^5 are attached may form a carbocyclic group substituted with one or more substituent(s) selected from the group consisting of a lower alkyl group, hydroxy group, a protected hydroxy group, a lower alkoxy group, an amino group optionally substituted with acyl, an ureido group

optionally substituted with lower alkyl, a lower alkylenedioxy group optionally substituted with oxo, and a cycloalkylidenedioxy group, and

R^6 is hydrogen atom or a lower alkyl group,

and a pro-drug thereof, and a salt thereof or

R^1 is nitro group, amino group, cyano group, a halo(lower)alkyl group or a halogen atom,

R^2 is an aryl group substituted with one ore more substituent(s) selected from the group consisting of a halogen atom, cyano group, a lower alkyl group and a lower alkoxy group,

A is a lower alkylene group,

and

R^3 is a saturated 3 to 7-membered, preferably 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) or 1 to 2 oxygen atom(s) optionally substituted with one or more substituent(s) selected from the group consisting of carbamoyl group, sulfamoyl group, a protected carboxy group and a lower alkyl group optionally substituted with hydroxy, or

a group of the formula : $-CR^4R^5R^6$ in which

R^4 and R^5 are each independently

a carbamoyl group or a lower alkyl group optionally substituted with one or more substituent(s) selected from the group consisting of hydroxy group and an amino group optionally substituted with acyl, protected carboxy, carbamoyl or lower alkylcarbamoyl, or

R^4 and R^5 together with the carbon atom to which R^4 and R^5 are attached may form a carbocyclic group optionally substituted with one or more substituent(s) selected from the group consisting of a lower alkyl group, hydroxy group, a protected hydroxy group, a lower alkoxy group, an amino group optionally substituted with acyl, an ureido group optionally substituted with lower alkyl, a lower alkylenedioxy group optionally substituted with oxo, and a cycloalkylidenedioxy group, and

R^6 is hydrogen atom or a lower alkyl group,

and their pro-drugs thereof, and salts thereof.

Still further preferred embodiments of the compounds [I] are those of the formula [I] wherein:

R^1 is cyano group or a halo(lower)alkyl group,

R^2 is a phenyl group substituted with one or two substituent(s) selected from the group consisting of a halogen atom, cyano group and a lower alkoxy group,

A is a lower alkylene group,

and

R^3 is a group of the formula : $-CR^4R^5R^6$ in which

R^4 and R^5 together with the carbon atom to which R^4 and R^5 are attached may form a carbocyclic group substituted with one or two substituent(s) selected from the group consisting of hydroxy group, a lower alkoxy group and a lower alkanoylamino group, and

R^6 is hydrogen atom,

and a pro-drug thereof, and a salt thereof or

R^1 is nitro group, amino group, cyano group, a halo(lower)alkyl group or a halogen atom,

R^2 is an aryl group substituted with cyano and optionally further substituted with halogen, cyano, lower alkyl or lower alkoxy,

A is a lower alkylene group,

and

R^3 is a saturated 3 to 7-membered, preferably 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) or 1 to 2 oxygen atom(s) optionally substituted with one or more substituent(s) selected from the group consisting of carbamoyl group, sulfamoyl group, a protected carboxy group and a lower alkyl group optionally substituted with hydroxy, or

a group of the formula : $-CR^4R^5R^6$ in which

R^4 and R^5 are each independently

a carbamoyl group or a lower alkyl group optionally substituted with one or more substituent(s) selected from the group consisting of hydroxy group and an

amino group optionally substituted with acyl, protected carboxy, carbamoyl or lower alkylcarbamoyl, or

R^4 and R^5 together with the carbon atom to which R^4 and R^5 are attached may form a carbocyclic group optionally substituted with one or more substituent(s) selected from the group consisting of a lower alkyl group, hydroxy group, a protected hydroxy group, a lower alkoxy group, an amino group optionally substituted with acyl, an ureido group optionally substituted with lower alkyl, a lower alkylenedioxy group optionally substituted with oxo, and a cycloalkylidenedioxy group, and

R^6 is hydrogen atom or a lower alkyl group,

and their pro-drugs thereof, and salts thereof.

The processes for preparing the object compounds [I] and the starting compounds of the present invention are explained in detail in the following.

Process 1

A compound [I] or its salt can be prepared by reacting a compound [II] or its salt with a compound [III] or its salt.

Suitable salts of the compounds [II] and [III] can be referred to the ones as exemplified for the compound [I].

This reaction is usually carried out in the presence of an inorganic or an organic base.

Suitable inorganic base may include an alkali metal [e.g., sodium or potassium], an alkali metal hydroxide [e.g., sodium hydroxide or potassium hydroxide], an alkali metal hydrogen carbonate [e.g., sodium hydrogen carbonate or potassium hydrogen carbonate], an alkali metal carbonate [e.g., sodium carbonate or potassium carbonate], an alkali earth metal carbonate [e.g., calcium carbonate], an alkali metal hydride [e.g., sodium hydride or potassium hydride] and the like.

Suitable organic base may include tri(lower)alkylamine [e.g., triethylamine or N,N-diisopropylethylamine], pyridine, alkyl lithiums [e.g., methyl lithium or butyl lithium], lithium diisopropylamide, lithium

hexamethyldisilazido and the like.

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g., methanol, ethanol or isopropyl alcohol], tetrahydrofuran, dioxane, toluene, methylene chloride, chloroform, pyridine, N,N-dimethylformamide or any other organic solvent which does not adversely affect the reaction, or a mixture thereof.

The reaction is preferably carried out at a temperature under cooling to warming. However, the reaction temperature is not limited.

Process 2

A compound [I] or its salt can be prepared by reacting a compound [IV] or its reactive derivative at the carboxy group or a salt thereof, with a compound [V] or its reactive derivative at the amino group or a salt thereof.

Suitable reactive derivatives at the carboxy group of the compound [IV] may include the acid chloride, azide, acid anhydride, activated amide, activated ester and the like.

Suitable acid anhydride may include anhydrides with an acid such as substituted phosphoric acid [e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid or halogenated phosphoric acid], dialkylphosphorous acid, sulfuric acid, thiosulfuric acid, alkanesulfonic acid [e.g., methanesulfonic acid or ethanesulfonic acid], alkanoic acid [e.g., pivalic acid, pentanoic acid or isopentanoic acid], aromatic carboxylic acid [e.g., benzoic acid, chlorobenzoic acid, fluorobenzoic acid or nitrobenzoic acid], or the like.

Suitable activated amide may include the imidazolylamide, 4-substituted imidazolylamide, dimethylpyrazolylamide, triazolylamide tetrazolylamide or the like.

Suitable activated ester may include the dimethyliminomethyl [$(CH_3)_2N^+=CH$-] ester, vinyl ester, propargyl ester, 4-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, pentafluorophenyl ester, methanesulfonylphenyl ester, phenyl thioester, p-nitrophenyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, 8-quinolyl thioester, an ester with a N-hydroxy compound [e.g., N,N-dimethylhydroxylamine, 1-hydroxy-2H-pyridone, N-

hydroxysuccinimide, N-hydroxybenzotriazole or N-hydroxyphthalimide] or the like.

Suitable reactive derivative at the amino group of the compound [V] may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound [V] with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound [V] with a silylating reagent such as trimethylsilylchloride, N,O-bis(trimethylsilyl)acetamide, N-trimethylsilylacetamide or the like.

Each reactive derivative of the compounds [IV] and [V] can optionally be selected from the above according to the kinds of the compounds [IV] and [V] to be used, respectively.

Suitable salts of the compounds [IV] and [V] and their reactive derivatives can be referred to the ones as exemplified for the compound [I].

When the compound [IV] is used in a free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of a condensing agent.

Suitable condensing agent may include carbodiimide [e.g., N,N-dicyclohexylcarbodiimide, N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide, or hydrochloride thereof], diphenylphosphinic azide, diphenylphosphinic chloride, diethylphosphoryl cyanide, bis(2-oxo-3-oxazolidinyl)phosphinic chloride, N,N'-carbonyldiimidazole, 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, cyanuric chloride or the like.

The reaction may be also carried out in the presence of an organic or inorganic base such as an alkali metal carbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorphorine or the like.

The reaction is usually carried out in a conventional solvent such as water, acetone, alcohol [e.g., methanol, ethanol or isopropyl alcohol], tetrahydrofuran, dioxane, toluene, methylene chloride, chloroform, N,N-dimethylformamide or any other organic solvent which does not adversely affect the reaction, or a mixture thereof.

The reaction is preferably carried out at a temperature under

cooling to warming. However, the reaction temperature is not limited.

Process 3

A compound [I-1] or its salt can be prepared by reacting a compound [VI] or its salt with a ketone compound [VII] or its salt in the presence of an inorganic acid [e.g., sulfuric acid or hydrogen chloride] or an organic acid [e.g., acetic acid] and a reducing agent.

Suitable salts of the compounds [VI] and [VII] can be referred to the ones as exemplified for the compound [I].

Suitable reducing agent may include sodium cyanoborohydride, sodium triacetoxyborohydride, sodium borohydride, borane-pyridine complex and the like.

The reaction is usually carried out in a conventional solvent such as alcohol [e.g., methanol or ethanol], tetrahydrofuran, dioxane, toluene or any other organic solvent which does not adversely affect the reaction, or a mixture thereof.

The reaction is preferably carried out at a temperature under cooling to ambient temperature. However, the reaction temperature is not limited.

Instead of the ketone compound[VII], its corresponding aldehyde may be used in this reaction.

Process 4

A compound [I-3] or its salt can be prepared by subjecting a compound [I-2] to a hydrolysis reaction.

The hydrolysis is preferably carried out in the presence of an acid.

Suitable acid may include an organic acid [e.g., formic acid, acetic acid, propionic acid, trichloroacetic acid or trifluoroacetic acid] or an inorganic acid [e.g., hydrochloric acid, hydrobromic acid, hydroiodic acid or sulfuric acid].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g., methanol or ethanol], xylene, diethylene glycol monomethyl ether, methylene chloride, tetrahydrofuran, dioxane, a mixture thereof or any other solvent which does not adversely influence the reaction. A

liquid acid can be also used as the solvent.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Process A

A compound [II] or its salt can be prepared by reacting a compound [VIII] or its reactive derivative at the carboxy group or a salt thereof, with a compound [V] or its reactive derivative at the amino group or a salt thereof.

Suitable reactive derivatives at the carboxy group of the compound [VIII] can be referred to the ones as exemplified for the compound [IV].

Suitable salts of the compound [VIII] and its reactive derivative can be referred to the ones as exemplified for the compound [I].

This reaction can be carried out in a similar manner to Process 2, and therefore, the reaction mode and reaction condition of this reaction are to be referred to those explained in Process 2.

Process B

(Step 1)

A compound [IVa] or its salt can be prepared by reacting a compound [IX] or its salt with a compound [III] or its salt.

Suitable salts of the compound [IVa] can be referred to the ones as exemplified for the compound [I].

Suitable salts of the compound [IX] can be referred to the acid addition salts as exemplified for the compound [I].

This reaction can be carried out in a similar manner to Process 1, and therefore, the reaction mode and reaction condition of this reaction are to be referred to those explained in Process 1.

(Step 2)

A compound [IV] or its salt can be prepared by subjecting a compound [IVa] or its salt to hydrolysis reaction.

The hydrolysis is preferably carried out in the presence of a base or an acid.

Suitable base may be the same as those exemplified in Process

1.

Suitable acid may include an organic acid [e.g., formic acid, acetic acid, propionic acid, trichloroacetic acid or trifluoroacetic acid] or an inorganic acid [e.g., hydrochloric acid, hydrobromic acid, hydroiodic acid or sulfuric acid].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g., methanol or ethanol], xylene, diethylene glycol monomethyl ether, methylene chloride, tetrahydrofuran, a mixture thereof or any other solvent which dose not adversely influence the reaction. A liquid base or acid can be also used as the solvent.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Process C

A compound [VI] or its salt can be prepared by reacting a compound [X] or its salt with a compound [V] or its reactive derivative at the amino group or a salt thereof.

Suitable salts of the compound [X] can be referred to the acid addition salts as exemplified for the compound [I].

This reaction is usually carried out in a conventional solvent such as acetone, tetrahydrofuran, dioxane, toluene, methylene chloride, chloroform, N,N-dimethylformamide or any other organic solvent which does not adversely affect the reaction, or a mixture thereof.

The reaction is preferably carried out at a temperature under cooling to amibient temperature. However, the reaction temperature is not limited.

The object compound [I] and the starting compounds can also be prepared by the methods of Examples mentioned below or similar manners thereto or conventional manners.

The compound obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, chromatography, reprecipitation or the like.

It is to be noted that the compound [I] and the other compounds may include one or more stereoisomer(s) and geometrical isomer(s) due

to asymmetric carbon atom(s) and double bond(s), and all of such isomer(s) and mixture thereof are included within the scope of this invention.

The compounds of the formula [I] may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

It is further to be noted that isomerization or rearrangement of the compounds [I] may occur by the effect of light, acid, base or the like, and the compounds obtained as the result of said isomerization or rearrangement are also included within the scope of the present invention.

The compound of the formula [I] and its salt can be in the form of a solvate, which is included within the scope of the present invention. The solvate preferably includes a hydrate and an ethanolate.

A pharmaceutically acceptable salt of the compound [I] can be prepared by treating a compound [I] with an appropriate base or acid in accordance with the conventional method.

Also included in the scope of invention are radiolabelled derivatives of compounds of formula [I] which are suitable for biological studies.

The compounds [I] and pharmaceutically acceptable salts thereof possess inhibitory activity of cGMP-PDE, especially PDE-V, relaxant activity of smooth muscle, bronchodilator activity, vasodilative activity, relaxant activity of the penile corpus cavernosum, inhibitory activity of smooth muscle cells proliferation, inhibitory activity of allergy, and so on.

The compounds [I] and pharmaceutically acceptable salts thereof, therefore, are useful for the treatment and/or prevention of various diseases, such as angina, hypertension, pulmonary hypertension, congestive heart failure, glomerular diseases [e.g., diabetic glomerulosclerosis], renal tubulo-interstitial diseases [e.g., nephropathy induced by tacrolimus or cyclosporin], renal failure, atherosclerosis, conditions of reduced blood vessel patency [e.g., post-percutaneous transluminal coronary angioplasty], peripheral vascular

disease, stroke, chronic reversible obstructive lung diseases [e.g., bronchitis, asthma [chronic asthma or allergic asthma]], allergic rhinitis, urticaria, glaucoma, diseases characterized by disorders of gut motility [e.g., irritable bowel syndrome], erectile dysfunction [e.g., organic erectile dysfunction or psychic erectile dysfunction], female sexual dysfunction, impotence, or diabetic complications [e.g., diabetic gangrene, diabetic arthropathy, diabetic glomerulosclerosis, diabetic dermopathy, diabetic neuropathy, diabetic cataract or diabetic retinopathy].

Further, the compounds [I] and pharmaceutically acceptable salts thereof are also useful for the treatment and/or prevention of micturition disorder, incontinence or storage of urine disorder such as the ones ascribed to nerve regressive affection, inflammation, injury, neoplasm, diabetes mellitus, cerebral vascular accident, surgery, prostatomegaly, urethra relaxation incompetence or dysuria.

It is to be noted that improvement of sexual performance is also included in the treatment of erectile dysfunction or impotence.

The compounds [I] and their salts of the present invention have much advantages, such as stronger activity, more suitable half-life, decreased adverse effect, or the like, compared to the known anthranilic acid derivatives having an inhibitory activity of cGMP-PDE, which are shown in the prior arts.

In order to exhibit the usefulness of the present invention, the activities of the compounds [I] are shown in the following.

Test Method

cGMP-Phosphodiesterase (PDE) assay

Human platelet cGMP-PDE was separated from other isozymes in human platelets by a modification of the method of Thompson et. al. [see Cyclic Nucleotide Phosphodiesterase (PDE), in Methods of Enzymatic analysis, Vol 4, p127-234, 1984]. In enzyme inhibition assays, the test compounds were dissolved in DMSO and then diluted with assay buffer (50 mM Tris-HCl, 0.077 mg/ml dithiothreitol and 10

mg/ml snake venom, 1 mM EGTA, pH 8.0), at final concentrations ranging from 10^{-10} to 10^{-6} M. Assays were performed at 0.1 μM substrate ([^{3}H]-cGMP) concentration, at 30 ℃ for 10 minutes using enzyme dilutions which gave 10-20% hydrolysis of substrate. Each assay was initiated by addition of substrate and terminated by addition of anion exchange resin (Dowex ® 1-X8, 250 mg/mg) followed by centrifugation for 10 minutes (3000 rpm, at 4 ℃). Radioactivity of supernatant (^{3}H-GMP) was assayed by liquid scintillation counting.

Test Result

Test Compound (Example No.)	Inhibitory Activity : IC_{50} (nM)
Example 1-(3)	<10
Example 5	<10
Example 16-(2)	<10
Example 41	<10
Example 53-(2)	<10
Example 55-(5)	<10
Example 58-(4)	<10
Example 64	<10
Example 74	<10
Example 78-(1)	<10
Example 84	<10
Example 87	<10
Example 99-(4)	<10

As shown in the above Table, the compounds [I] of the present invention have superior inhibitory activity against cGMP-PDE.

The compound [I] or its salt can be administered alone or in a form of a mixture, preferably, with a pharmaceutical vehicle or carrier.

The active ingredient of this invention can be used in a form of a pharmaceutical preparation, for example, in solid, semisolid or liquid

form, which contains a compound [I], as an active ingredient, in admixture with an organic or inorganic carrier r excipient suitable for oral, parenteral such as intravenous, intramuscular, subcutaneous, intracavernous or intraarticular, external such as topical, intrarectal, transvaginal, inhalant, ophthalmic, nasal or hypoglossal applications. The active ingredient may be compounded, for example, with the conventional non-toxic, pharmaceutically acceptable carriers or excipients for ointment, cream, plaster, tablets, pellets, capsules, suppositories, solution, emulsion, suspension, aerosols, pills, powders, syrups, injections, troches, cataplasms, aromatic waters, lotions, buccal tablets, sublingual tablets, nasal drops and any other form suitable for use. The carriers which can be used are water, olive oil, saline, wax, glucose, lactose, gum acacia, gelatin, mannitol, starch paster, magnesium trisilicate, talc, corn starch, keratin, paraffin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations in solid, semisolid or liquid form, and in addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. The active compound is included in a pharmaceutical composition in an effective amount sufficient to produce the desired effect upon the process or condition of the diseases.

The active ingredient may be compounded into , for example, preparations for oral application, preparations for injection, preparations for external application, preparations for inhalation, preparations for application to mucous membranes [e.g., oral mucous membrane, fascia penis, facies urethralis penis, etc.].

Mammals which may be treated by the present invention include humans, livestock mammals such as cows, horses, etc., and domestic animals such as dogs, cats, rats, etc., preferably humans.

While the therapeutically effective amount of a compound [I] varies depending upon the age and condition of each individual patient to be treated, in case of the systemic administration, a daily dose of about 0.01-1000 mg, preferably 0.1-500 mg and more preferably 0.5-100 mg of the active ingredient is generally given for treating the diseases, and an average single dose of about 0.2-0.5 mg, 1 mg, 5 mg, 10 mg, 50 mg, 100 mg, 250 mg and 500 mg is generally administered. Daily doses

for chronic administration in humans will be in the range of about 0.3 mg/body to 1,000 mg/body.

The patents, patent applications and publications cited herein above are incorporated by reference.

BEST MODE FOR CARRYING OUT THE INVENTION

The following Examples are given only for the purpose of illustrating the present invention in more detail.

Example 1

(1) To a solution of ethyl 2-amino-5-nitrobenzoate (5.00 g), cyclopentanone (9.00 g) and sodium borohydride (4.05 g) in anhydrous tetrahydrofuran (100 ml) was added sulfuric acid (6 ml) under ice-water cooling. The mixture was stirred for 9 hours at 0°C and then for 15 hours at ambient temperature. The mixture was neutralized with an aqueous saturated sodium bicarbonate solution and extracted with ethyl acetate. The extract was washed with water and brine, dried over magnesium sulfate and evaporated *in vacuo*. The residue was purified by a silica gel column chromatography eluting with a mixture of hexane and ethyl acetate (5:1). The obtained product was triturated with hexane to give ethyl 2-cyclopentylamino-5-nitrobenzoate as a yellow powder (5.94 g).
NMR ($CDCl_3$, δ): 1.41 (3H, t, J=7Hz), 1.58-1.90 (6H, m), 2.10 (2H, m), 3.96 (1H, m), 4.36 (2H, q, J=7Hz), 6.70 (1H, d, J=8Hz), 8.18 (1H, dd, J=4, 8Hz), 8.67 (1H, br), 8.87 (1H, d, J=4Hz)

(2) 2-Cyclopentylamino-5-nitrobenzoic acid (5.16 g) was obtained as an yellow powder from ethyl 2-cyclopentylamino-5-nitrobenzoate (5.94 g) in a similar manner to Example 11-(2).
NMR (DMSO-d_6, δ): 1.47 (2H, m), 1.58-1.78 (4H, br), 2.10 (2H, br), 4.05 (1H, m), 6.93 (1H, d, J=8Hz), 8.18 (1H, dd, J=4, 8Hz), 8.65 (1H, d, J=4Hz), 8.83 (1H, br)

(3) To a mixture of 2-(cyclopentylamino)-5-nitrobenzoic acid (150 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (172 mg),

1-hydroxybenzotriazole (121 mg) in anhydrous dimethylformamide (3 ml) was added pentylamine (62.7 mg) and the mixture was stirred at ambient temperature for 2 hours. The mixture was partitioned between ethyl acetate and water. The separated organic layer was washed with a saturated sodium bicarbonate solution, water and brine, dried over magnesium sulfate, and evaporated *in vacuo*. The residue was crystallized from hexane to give 2-(cyclopentylamino)-5-nitro-*N*-pentylbenzamide (165 mg) as a yellow powder.

NMR ($CDCl_3$, δ): 0.93 (3H, t, J=7Hz), 1.31-1.48 (4H, br), 1.55-1.90 (8H, br), 1.97-2.18 (2H, br), 3.40 (2H, q, J=7Hz), 3.83-3.97 (1H, br), 6.29 (1H, br), 6.67 (1H, d, J=8Hz), 8.15 (1H, dd, J=2, 8Hz), 8.31 (1H, d, J=2Hz), 8.83 (1H, br)

Example 2

2-(Cyclopentylamino)-*N*-heptyl-5-nitrobenzamide (200 mg) was prepared from 2-(cyclopentylamino)-5-nitrobenzoic acid (150 mg) and heptylamine (82.9 mg) in a similar manner to Example 1-(3) as a yellow powder.

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=7Hz), 1.22-1.47 (8H, br), 1.55-1.90 (8H, br), 2.02-2.17 (2H, br), 3.39 (2H, q, J=7Hz), 3.85-3.96 (1H, br), 6.22(1H, br), 6.67 (1H, d, J=8Hz), 8.15 (1H, dd, J=2, 8Hz), 8.30 (1H, d, J=2Hz), 8.82 (1H, br)

Example 3

N-Butyl-2-(cyclopentylamino)-5-nitrobenzamide (158 mg) was prepared from 2-(cyclopentylamino)-5-nitrobenzoic acid (150 mg) and butylamine (52.6 mg) in a similar manner to Example 1-(3) as a yellow powder.

NMR ($CDCl_3$, δ): 0.98 (3H, t, J=7Hz), 1.38-1.49 (2H, m), 1.55-1.89 (8H, br), 2.02-2.17 (2H, br), 3.41 (2H, q, J=7Hz), 3.84-3.97 (1H, br), 6.24 (1H, br), 6.67 (1H, d, J=8Hz), 8.14 (1H, dd, J=2, 8Hz), 8.30 (1H, d, J=2Hz), 8.82 (1H, br)

Example 4

2-(Cyclopentylamino)-5-nitro-*N*-propylbenzamide (162 mg) was prepared from 2-(cyclopentylamino)-5-nitrobenzoic acid (150 mg) and

propylamine hydrochloride (68.7 mg) in a similar manner to Exampl 1-(3) as a yellow powder.

NMR ($CDCl_3$, δ): 1.01 (3H, t, J=7Hz), 1.56-1.90 (8H, br), 2.03-2.17 (2H, br), 3.35-3.46 (2H, m), 3.85-3.97 (1H, br), 6.28 (1H, br), 6.67 (1H, d, J=8Hz), 8.14 (1H, dd, J=2, 8Hz), 8.32 (1H, d, J=2Hz), 8.83 (1H, br)

Example 5

N-Cyclohexylmethyl-2-(cyclopentylamino)-5-nitrobenzamide (183 mg) was prepared from 2-(cyclopentylamino)-5-nitrobenzoic acid (150 mg) and aminomethylcyclohexane (81.4 mg) in a similar manner to Example 1-(3) as a yellow powder.

NMR ($CDCl_3$, δ): 0.93-1.10 (2H, br), 1.11-1.40 (3H, br), 1.55-1.88 (12H, br), 2.00-2.16 (2H, br), 3.26 (2H, t, J=7Hz), 3.85-3.97 (1H, m), 6.28 (1H, br), 6.67 (1H, d, J=8Hz), 8.14 (1H, dd, J=2, 8Hz), 8.30 (1H, d, J=2Hz), 8.82 (1H, br)

Example 6

2-(Cyclopentylamino)-*N*-(1-naphthylmethyl)-5-nitrobenzamide (225 mg) was prepared from 2-(cyclopentylamino)-5-nitrobenzoic acid (150 mg) and 1-aminomethylnaphthalene (113 mg) in a similar manner to Example 1-(3) as a yellow powder.

NMR ($CDCl_3$, δ): 1.60-1.77 (4H, br), 1.77-1.92 (2H, br), 2.05-2.20 (2H, br), 3.87-4.00 (1H, br), 5.05 (2H, d, J=7Hz), 6.40 (1H, br), 6.69 (1H, d, J=8Hz), 7.43-7.60 (4H, m), 7.83-7.93 (2H, m), 8.03 (1H, d, J=8Hz), 8.12 (1H, dd, J=2, 8Hz), 8.21 (1H, d, J=2Hz), 8.88 (1H, br)

Example 7

2-(Cyclopentylamino)-*N*-(3,4-dimethoxybenzyl)-5-nitrobenzamide (150 mg) was prepared from 2-(cyclopentylamino)-5-nitrobenzoic acid (100 mg) and 3,4-dimethoxybenzylamine (80.2 mg) in a similar manner to Example 1-(3) as a yellow powder.

NMR ($CDCl_3$, δ): 1.59-1.85 (6H, m), 2.03-2.15 (2H, m), 3.89 (3H, s), 3.90 (3H, s), 3.93 (1H, m), 4.52 (2H, d, J=7Hz), 6.50 (1H, br), 6.68 (1H, d, J=8Hz), 6.85-6.93 (3H, m), 8.14 (1H, dd, J=2, 8Hz), 8.31 (1H, d, J=2Hz), 8.88 (1H, br)

Example 8

2-(Cyclopentylamino)-5-nitro-*N*-(4-pyridylmethyl)benzamide (130 mg) was prepared from 2-(cyclopentylamino)-5-nitrobenzoic acid (100 mg) and 4-aminomethylpyridine (51.9 mg) in a similar manner to Example 1-(3) as a yellow powder.

NMR (DMSO-d_6, δ): 1.37-1.50 (2H, m), 1.54-1.73 (4H, m), 1.96-2.10 (2H, m), 3.96 (1H, m), 4.47 (2H, d, J=7Hz), 6.89 (1H, d, J=8Hz), 7.31 (2H, d, J=7Hz), 8.16 (1H, dd, J=2, 8Hz), 8.52 (2H, d, J=7Hz), 8.70 (1H, d, J=2Hz), 9.13 (1H, d, J=8Hz), 9.48 (1H, br)

Example 9

N-Benzyl-2-(cyclopentylamino)-5-nitrobenzamide (1.36 g) was prepared from 2-(cyclopentylamino)-5-nitrobenzoic acid (1.04 g) and benzylamine (534 mg) in a similar manner to Example 1-(3) as a yellow powder.

NMR ($CDCl_3$, δ): 1.58-1.90 (6H, br), 2.03-2.15 (2H, br), 3.90 (1H, m), 4.59 (2H, d, J=7Hz), 6.52 (1H, br), 6.69 (1H, d, J=8Hz), 7.28-7.40 (5H, m), 8.13 (1H, dd, J=2, 8Hz), 8.32 (1H, d, J=2Hz), 8.87 (1H, br)

Example 10

(1) 2-Amino-*N*-hexyl-5-nitrobenzamide (1.09 g) was obtained as an yellow powder from 5-nitroisatoic anhydride (1.00 g) and hexylamine (583 mg) in a similar manner to Example 14-(1).

NMR (DMSO-d_6, δ): 0.85 (3H, br), 1.30 (6H, br), 1.52 (2H, br), 3.20 (2H, m), 6.78 (1H, d, J=8Hz), 7.75 (2H, br), 8.02 (1H, dd, J=4, 8Hz), 8.48 (1H, d, J=4Hz), 8.67 (1H, br)

(2) To a solution of 2-amino-*N*-hexyl-5-nitrobenzamide (200 mg), cyclopentanone (133 mg) and sodium borohydride (42.8 mg) in anhydrous tetrahydrofuran (6 ml) was added sulfuric acid (10 drops) under ice-water cooling, and the mixture was stirred at ambient temperature for 5 hours. The mixture was neutralized with a saturated sodium bicarbonate solution and extracted with ethyl acetate. The extract was washed with water and brine, dried over magnesium sulfate, and evaporated *in vacuo*. The residue was purified by a silica gel column chromatography eluting with a mixture of hexane and ethyl acetate (5:1). The crude product was triturated with hexane to give 2-(cyclohexylamino)-*N*-hexyl-5-nitrobenzamide (23.0 mg) as a yellow

powder.

NMR ($CDCl_3$, δ): 0.90 (3H, br), 1.25-1.47 (8H, br), 1.53-1.78 (6H, br), 1.78 (2H, br), 2.00 (2H, br), 3.38 (2H, dt, J=7, 7Hz), 3.40 (1H, br), 6.21 (1H, br), 6.65 (1H, d, J=8Hz), 8.12 (1H, dd, J=4, 8Hz), 8.29 (1H, d, J=4Hz), 8.83 (1H, br)

Example 11

(1) Methyl 5-cyano-2-cyclopentylaminobenzoate (438 mg) was prepared from methyl 2-amino-5-cyanobenzoate (500 mg) and cyclopentanone (716 mg), in a similar manner to Example 10-(2) as a colorless powder.

NMR ($CDCl_3$, δ): 1.57-1.85 (6H, m), 2.00-2.13 (2H, m), 3.88 (3H, s), 3.89 (1H, m), 6.72 (1H, d, J=8Hz), 7.50 (1H, d, J=8Hz), 8.18 (1H, s), 8.34 (1H, br)

(2) A mixture of methyl 5-cyano-2-cyclopentylaminobenzoate (400 mg), methanol (20 ml) and 1*N* sodium hydroxide solution (5 ml) was heated under reflux for 1 hour. The reaction mixture was acidified with 1*N*-hydrochloric acid to pH 4, and the organic solvent was removed by evaporation. The aqueous residue was diluted with water and extracted with ethyl acetate. The extract was washed with water and brine, dried over magnesium sulfate, and evaporated *in vacuo*. The residue was triturated with hexane to give 2-cyclopentylamino-5-cyanobenzoic acid (354 mg) as a pale yellow powder.

NMR (DMSO-d_6, δ): 1.38-1.53 (2H, m), 1.53-1.78 (4H, m), 1.95-2.10 (2H, m), 3.96 (1H, m), 6.89 (1H, d, J=8Hz), 7.68 (1H, dd, J=2, 8Hz), 8.09 (1H, d, J=2Hz), 8.51 (2H, br)

(3) 5-Cyano-2-(cyclopentylamino)-*N*-hexylbenzamide (135 mg) was prepared from 5-cyano-2-(cyclopentylamino)benzoic acid (100 mg) and hexylamine (52.7 mg) in a similar manner to Example 1-(3) as a colorless powder.

NMR ($CDCl_3$, δ): 0.90 (3H, br), 1.28-1.47 (6H, br), 1.51-1.84 (8H, br), 1.97-2.09 (2H, m), 3.38 (2H, m), 3.83 (1H, m), 6.09 (1H, br), 6.67 (1H, d, J=8Hz), 7.47 (1H, d, J=8Hz), 7.59 (1H, s), 8.32 (1H, br)

Example 12

(1) 2-Fluoro-*N*-hexyl-5-triflu romethylbenzamide (604 mg) was prepared from 2-fluoro-5-trifluoromethylbenzoic acid (500 mg) and hexylamine (292 mg) in a similar manner to Example 1-(3) as a colorless powder.

NMR ($CDCl_3$, δ): 0.90 (3H, br), 1.25-1.48 (6H, br), 1.55-1.75 (2H, br), 3.49 (2H, m), 6.69 (1H, br), 7.27 (1H, m), 7.73 (1H, m), 8.41 (1H, dd, J=2, 8Hz)

(2) To a solution of 2-fluoro-*N*-hexyl-5-trifluoromethylbenzamide (218 mg) in anhydrous pyridine (4 ml) was added cyclopentylamine (127 mg) and the mixture was stirred at 100°C for 18 hours. The mixture was partitioned between ethyl acetate and water. The separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated *in vacuo*. The residue was purified by a silica gel column chromatography eluting with a mixture of ethyl acetate and n-hexane (1:5). The product was triturated with n-hexane to give 2-(cyclopentylamino)-*N*-hexyl-5-trifluoromethylbenzamide (128 mg) as a white powder.

NMR ($CDCl_3$, δ): 0.87 (3H, br), 1.25-1.85 (14H, br), 1.95-2.10 (2H, br), 3.21 (2H, m), 3.83 (1H, m), 6.83 (1H, d, J=8Hz), 7.53 (1H, dd, J=2, 8Hz), 7.86 (1H, s), 8.44 (1H, d, J=8Hz), 8.56 (1H, br)

Example 13

(1) 2-(*trans*-4-Aminocyclohexylamino)-*N*-(3,4-dimethoxybenzyl)-5-nitrobenzamide (12.3 g) was obtained from *N*-(3,4-dimethoxybenzyl)-2-fluoro-5-nitrobenzamide (10.0 g) and *trans*-1,4-diaminocyclohexane (10.2 g) in a similar manner to Example 12-(2).

NMR (DMSO-d_6, δ): 1.10-1.38 (4H, br), 1.72-1.82 (2H, br), 1.94-2.05 (2H, br), 2.60 (1H, br), 3.46 (1H, br), 3.73 (3H, s), 3.74 (3H, s), 4.36 (2H, d, J=7Hz), 6.83-6.95 (4H, m), 8.10 (1H, dd, J=4, 8Hz), 8.59 (1H, d, J=4Hz), 9.01 (1H, d, J=8Hz), 9.31 (1H, br)

(2) To a solution of 2-(*trans*-4-aminocyclohexylamino)-*N*-(3,4-dimethoxybenzyl)-5-nitrobenzamide (150 mg) in dichloromethane (8 ml) was added ethyl isocyanate (5 drops) and the mixture was stirred at ambient temperature for 2 hours. After evaporation of the solvent, the residue was triturated with ethyl acetate to give *N*-(3,4-

dimethoxybenzyl)-2-[*trans*-4-(3-ethylureido)cyclohexyl-amino]-5-nitrobenzamide (150 mg) as a yellow powder.
NMR (DMSO-d_6, δ): 0.97 (3H, t, J=7Hz), 1.16-1.42 (4H, br), 1.78-1.90 (2H, br), 1.95-2.06 (2H, br), 2.94-3.08 (2H, m), 3.35-3.45 (1H, br), 3.45-3.57 (1H, br), 3.73 (3H, s), 3.74 (3H, s), 4.38 (2H, d, J=7Hz), 5.65 (1H, br), 5.73 (1H, d, J=8Hz), 6.80-6.98 (4H, m), 8.11 (1H, dd, J=2, 8Hz), 8.60 (1H, d, J=2Hz), 9.03 (1H, d, J=8Hz), 9.32 (1H, br)

Example 14

(1) A mixture of 5-bromoisatoic anhydride (1.0 g) and hexylamine (502 mg) in *N,N*-dimethylformamide (10 ml) was stirred for 4 hours at 20°C. The mixture was partitioned between ethyl acetate and water. The separated organic layer was washed with water and brine, dried over magnesium sulfate, and evaporated. The residue was purified by a silica gel column chromatography eluting with chloroform and recrystallization from a mixture of ethyl acetate and n-hexane to give 2-amino-5-bromo-*N*-hexylbenzamide (376 mg) as colorless crystals.
NMR ($CDCl_3$, δ): 0.90 (3H, t, J=7Hz), 1.25-1.45 (6H, m), 1.55-1.65 (2H, m), 3.38 (2H, q, J=7Hz), 5.49 (2H, brs), 5.97 (1H, brs), 6.57 (1H, d, J=9Hz), 7.26 (1H, dd, J=2, 9Hz), 7.38 (1H, d, J=2Hz)

(2) To a mixture of 2-amino-5-bromo-*N*-hexylbenzamide (350 mg), cyclopentanone (148 mg) and sodium borohydride (66.4 mg) in tetrahydrofuran (3.5 ml) was added sulfuric acid (172 mg) at 20°C. After stirring at the same temperature for 1.5 hours, the mixture was partitioned between ethyl acetate and a saturated sodium bicarbonate solution. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated *in vacuo*. The residue was crystallized from n-hexane to give 5-bromo-2-cyclopentylamino-*N*-hexylbenzamide (269 mg) as a white powder.
mp: 86-87°C
NMR ($CDCl_3$, δ): 0.90 (3H, t, J=7Hz), 1.30-1.45 (6H, m), 1.45-1.70 (8H, m), 1.95-2.05 (2H, m), 3.36 (2H, q, J=7Hz), 3.76 (2H, sextet, J=7Hz), 5.96 (1H, brs), 6.58 (1H, d, J=9Hz), 7.32 (1H, dd, J=2, 9Hz), 7.37 (1H, d, J=2Hz), 7.53 (1H, d, J=7Hz)

Example 15

(1) A mixture of (*S*)-2-benzyloxycarbonylamino-1,4-bis(methanesulfonyloxy)butane (1.49 g) and 2-amin ethanol (2.3 g) was stirred for 2 hours at 40°C. The mixture was concentrated *in vacuo*, and the residue was partitioned between chloroform and water. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo* to give (*S*)-3-benzyloxycarbonylamino-1-(2-hydroxyethyl)pyrrolidine (1.13 g) as an oil.
NMR (DMSO-d_6, δ): 1.54 (1H, m), 2.02 (1H, m), 2.32 (2H, dd, J=6, 9Hz), 2.35-2.60 (4H, m), 2.69 (1H, dd, J=8,9Hz), 3.44 (2H, q, J=6Hz), 3.94 (1H, m), 4.40 (1H, t, J=6Hz), 5.00 (2H, s), 7.25-7.45 (6H, m)

(2) A mixture of (*S*)-3-benzyloxycarbonylamino-1-(2-hydroxyethyl)pyrrolidine (1.19 g) and palladium hydroxide (100 mg) in a mixture of methanol (10 ml) and acetic acid (5 ml) was hydrogenated under hydrogen atmosphere (3.5 atm) for 6 hours at between 30 and 35°C. The mixture was filtered through a celite pad and washed with methanol. The filtrate and the washings were combined and concentrated *in vacuo* to give (*S*)-3-amino-1-(2-hydroxyethyl)pyrrolidine diacetate (1.26 g) as a syrup.
NMR (DMSO-d_6, δ): 1.64 (1H, m), 1.90 (6H, s), 2.09 (1H, m), 2.35 (1H, m), 2.45-2.70 (4H, m), 2.79 (1H, m), 3.17 (1H, s), 3.48 (2H, t, J=6Hz), 3.60 (1H, m)

(3) To a solution of 5-bromo-2-fluorobenzaldehyde (10 g) in dimethylformamide (60 ml) were added zinc cyanide (6.92 g) and tetrakis(triphenylphosphine)palladium(0) (2.28 g), and the mixture was stirred at 80°C for 6 hours. The resulting mixture was diluted with ethyl acetate and washed successively with water and brine. The organic layer was dried over sodium sulfate and evaporated *in vacuo*. The residue was subjected to a silica gel column chromatography eluting with a mixture of n-hexane and ethyl acetate (3:1) to give 5-cyano-2-fluorobenzaldehyde (5.3 g) as a solid substance.
NMR (DMSO-d_6, δ): 7.35 (1H, t, J=9Hz), 7.91 (1H, m), 8.22 (1H, dd, J=2, 7Hz), 10.36 (1H, s)

(4) To a solution of 5-cyano-2-fluorobenzaldehyde (145 mg) in acetonitrile (2 ml) were added a sodium dihydrogenphosphate aqueous

solution (23 mg in 1 ml water) and 30% hydrogen peroxide (0.09 ml). To the resulting mixture was added dropwise a sodium chlorite aqueous solution (126 mg in 1 ml water) for an hour at 0°C. The mixture was stirred for an hour at ambient temperature, then a small amount of sodium sulfite was added. The mixture was diluted with ethyl acetate and washed successively with 1*N*-hydrochloric acid and brine. The organic layer was dried over sodium sulfate and evaporated *in vacuo*. The residue was triturated with diisopropyl ether to give 5-cyano-2-fluorobenzoic acid (137 mg) as a solid substance.
NMR (DMSO-d_6, δ): 7.29 (1H, t, J=9Hz), 7.83 (1H, m), 8.32 (1H, dd, J=2, 7Hz)

(5) 5-Cyano-*N*-(3,4-dimethoxybenzyl)-2-fluorobenzamide (228 mg) was obtained from 5-cyano-2-fluorobenzoic acid (130 mg) and veratrylamine (0.14 ml) in a similar manner to Example 1-(3).
NMR (DMSO-d_6, δ): 3.73 (3H, s), 3.75 (3H, s), 4.40 (2H, d, J=6Hz), 6.82-6.96 (3H, m), 7.56 (1H, t, J=9Hz) 8.04 (1H, m), 8.11 (1H, dd, J=2, 6Hz), 9.02 (2H, t, J=6Hz)

(6) To a solution of 5-cyano-*N*-(3,4-dimethoxybenzyl)-2-flurobenzamide (150 mg) in anhydrous pyridine (4 ml) were added (*S*)-3-amino-1-(2-hydroxyethyl)pyrrolidine diacetate (311 mg) and triethylamine (290 mg), and the mixture was stirred for 24 hours at 100°C. After evaporation of the solvent, the residue was partitioned between ethyl acetate and a saturated sodium bicarbonate solution. The separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated *in vacuo*. The residue was purified by a preparative thin layer chromatography on silica gel developed with a mixture of chloroform, methanol and 28% ammonium hydroxide (100:10:1). The obtained product was crystallized from a mixture of propanol and diisopropyl ether to give 5-cyano-*N*-(3,4-dimethoxybenzyl)-2-[(*S*)-1-(2-hydroxyethyl)pyrrolidin-3-ylamino]benzamide (87 mg) as colorless crystals.
NMR (DMSO-d_6, δ): 1.48 (1H, m), 2.28 (1H, m), 2.35-2.65 (4H, m), 2.72 (1H, m), 2.80 (1H, dd, J=7, 9Hz), 3.47 (2H, q, J=6Hz), 3.72 (3H, s), 3.74 (3H, s), 4.03 (1H, m), 4.34 (2H, d, J=6Hz), 4.46 (1H, t, J=6Hz), 6.76 (1H, d, J=9Hz), 6.83 (1H, dd, J=2, 9Hz), 6.91 (1H, d, J=9Hz), 6.94 (1H, d, J=2Hz),

7.63 (1H, dd, J=2, 9Hz), 8.05 (1H, d, J=2Hz), 8.76 (1H, d, J=7Hz), 9.02 (1H, t, J=6Hz)

Example 16

(1) *N*-(3-Chloro-4-methoxybenzyl)-2-fluoro-5-(trifluoromethyl)-benzamide (2.92 g) was obtained from 2-fluoro-5-(trifluoromethyl)benzoic acid (1.76 g) and 3-chloro-4-methoxybenzylamine (1.45 g) in a similar manner to Example 1-(3).
NMR (DMSO-d_6, δ): 3.83 (3H, s), 4.41 (2H, d, J=6Hz), 7.13 (1H, d, J=9Hz), 7.29 (1H, dd, J=2, 8Hz), 7.41 (1H, d, J=2Hz), 7.58 (1H, t, J=9Hz), 7.93 (1H, m), 7.97 (1H, d, J=8Hz), 9.08 (1H, t, J=6Hz)

(2) *N*-(3-Chloro-4-methoxybenzyl)-2-[(*S*)-1-(2-hydroxyethyl)pyrrolidin-3-ylamino]-5-trifluromethylbenzamide (41 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-2-fluoro-5-trifluromethylbenzamide (150 mg) and (*S*)-3-amino-1-(2-hydroxyethyl)pyrrolidine diacetate (311 mg) in a similar manner to Example 15-(6) as an amorphous powder.
NMR (DMSO-d_6, δ): 1.49 (1H, m), 2.28 (1H, m), 2.36-2.57 (4H, m), 2.71 (1H, m), 2.83 (1H, dd, J=7, 12Hz), 3.48 (2H, q, J=5Hz), 3.83 (3H, s), 4.01 (1H, m), 4.36 (2H, d, J=6Hz), 4.45 (1H, t, J=5Hz), 6.80 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.26 (1H, dd, J=2, 9Hz), 7.37 (1H, d, J=2Hz), 7.55 (1H, brd, J=9Hz), 7.96 (1H, brs), 8.56 (1H, d, J=7Hz), 9.13 (1H, t, J=6Hz)

Example 17

(1) A solution of di-*tert*-butyl dicarbonate (5.44 g) in dioxane (10 ml) was added dropwise to a solution of (*S*)-3-benzyloxycarbonylaminopyrrolidine (3.66 g) in dioxane (10 ml) under cooling on an ice bath. The reaction mixture was stirred at ambient temperature overnight, then the reaction was quenched by addition of 3-(*N*,*N*-dimethylamino)propylamine (5 ml). The mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and 3.6% hydrochloric acid. The organic layer was washed with an aqueous saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography eluting with 30% ethyl acetate in n-hexane to give (*S*)-3-benzyloxycarbonylamino-1-*tert*-butoxycarbonylpyrrolidine (1.26 g) as an oil.

NMR ($CDCl_3$, δ): 1.45 (9H, s), 1.84 (1H, m), 2.14 (1H, m), 3.20 (1H, m), 3.33-3.50 (2H, m), 3.61 (1H, dd, J=2, 10Hz), 4.25 (1H, m), 4.85 (1H, m), 5.10 (2H, s), 7.27-7.41 (5H, m)

(2) (S)-3-Amino-1-*tert*-butoxycarbonylpyrrolidine (2.49 g) was obtained as a syrup from (*S*)-3-benzyloxycarbonylamino-1-*tert*-butoxycarbonyl-pyrrolidine (4.10 g) in a similar manner to Example 21-(3).
NMR (DMSO-d_6, δ): 1.39 (9H, s), 1.57 (1H, m), 1.88 (1H, m), 2.89 (1H, dd, J=5, 11Hz), 3.00-3.40 (3H, m), 3.42 (1H, m)

(3) 2-[(*S*)-1-*tert*-Butoxycarbonyl)pyrrolidin-3-ylamino]-5-cyano-*N*-(3,4-dimethoxybenzyl)benzamide (368 mg) was obtained as an amorphous powder from 5-cyano-*N*-(3,4-dimethoxybenzyl)-2-fluorobenzamide (500 mg) and (*S*)-3-amino-1-*tert*-butoxycarbonylpyrrolidine (593 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 1.82 (1H, m), 2.20 (1H, m), 3.10 (1H, m), 3.25-3.45 (2H, m), 3.61 (1H, m), 3.72 (3H, s), 3.74 (3H, s), 4.18 (1H, m), 4.35 (2H, d, J=6Hz), 6.84 (1H, dd, J=2, 8Hz), 6.80-6.94 (3H, m), 7.66 (1H, dd, J=2, 8Hz), 8.09 (1H, d, J=2Hz), 8.82 (1H, d, J=7Hz), 9.05 (1H, t, J=6Hz)

(4) 5-Cyano-*N*-(3,4-dimethoxybenzyl)-2-[(*S*)-3-pyrrolidinylamino]-benzamide (201 mg) was obtained as an amorphous powder from 2-[(*S*)-1-(*tert*-butoxycarbonyl)-pyrrolidin-3-ylamino]-5-cyano-*N*-(3,4-dimethoxybenzyl)benzamide (277 mg) in a similar manner to Example 23-(2).
NMR (DMSO-d_6, δ): 1.50 (1H, m), 2.11 (1H, m), 2.57 (1H, dd, J=4, 10Hz), 2.70-2.95 (2H, m), 3.13 (1H, dd, J=6, 10Hz), 3.72 (3H, s), 3.74 (3H, s), 3.96 (1H, m), 4.34 (2H, d, J=6Hz), 6.78-6.94 (4H, m), 7.64 (1H, dd, J=2, 8Hz), 8.06 (1H, d, J=2Hz), 8.72 (1H, d, J=7Hz) 9.02 (1H, t, J=6Hz)

(5) A solution of potassium cyanate (85.3 mg) in water (2 ml) was added to a solution of 5-cyano-*N*-(3,4-dimethoxybenzyl)-2-[(*S*)-3-pyrrolidinylamino]benzamide (200 mg) in a mixture of dioxane (1.5 ml) and 1*N*-hydrochloric acid (0.53 ml), and the reaction mixture was stirred for 1.5 hours at 20°C. The mixture was concentrated *in vacuo*, and the residue was partitioned between ethyl acetate and water. The organic

layer was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was purified by a thin layer chromatography developed with 10% methanol in chloroform and recrystallized from a mixture of 2-propanol and water to give 2-[(*S*)-1-carbamoylpyrrolidin-3-ylamino]-5-cyano-*N*-(3,4-dimethoxybenzyl)benzamide (50 mg) as colorless crystals.
NMR (DMSO-d_6, δ): 1.83 (1H, m), 2.20 (1H, m), 3.12 (1H, dd, J=4, 10Hz), 3.20-3.45 (2H, m), 3.57 (1H, dd, J=6, 10Hz), 3.72 (3H, s), 3.74 (3H, s), 4.19 (1H, m), 4.35 (2H, d, J=6Hz), 5.80 (2H, s), 6.84 (1H, dd, J=2, 8Hz), 6.87-6.95 (3H, m), 7.66 (1H, dd, J=2, 8Hz), 8.09 (1H, d, J=2Hz), 8.83 (1H, d, J=7Hz), 9.05 (1H, t, J=6Hz)

Example 18

A mixture of 5-cyano-*N*-(3,4-dimethoxybenzyl)-2-[(*S*)-3-pyrrolidinylamino]benzamide (150 mg) and sulfamide (76 mg) in ethylene glycol dimethyl ether (3 ml) was refluxed overnight. The mixture was concentrated *in vacuo*, and the residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was purified by a preparative thin layer chromatography eluting with 5% methanol in chloroform. The crude crystals were suspended in hot 2-propanol, cooled with stirring, collected and washed with 2-propanol to give 2-[(*S*)-1-aminosulfonylpyrrolidin-3-ylamino]-5-cyano-*N*-(3,4-dimethoxybenzyl)benzamide (100 mg) as colorless crystals.
NMR (DMSO-d_6, δ): 1.79 (1H, m), 2.29 (1H, m), 2.94 (1H, dd, J=5, 10Hz), 3.15-3.30 (2H, m), 3.51 (1H, dd, J=7, 10Hz), 3.72 (3H, s), 3.74 (3H, s), 4.22 (1H, m), 4.36 (2H, br), 6.80-6.95 (6H, m), 7.67 (1H, dd, J=2, 9Hz), 8.10 (1H, d, J=2Hz), 8.85 (1H, br), 9.07 (1H, br)

Example 19

Sodium triacetoxyborohydride (125 mg) and acetic acid (36 mg) were added to a mixture of 5-cyano-*N*-(3,4-dimethoxybenzyl)-2-[(*S*)-3-pyrrolidinylamino]benzamide (150 mg) and paraformaldehyde (36 mg) in tetrahydrofuran (3 ml). The reaction mixture was stirred at ambient temperature for 3 hours, then sodium triacetoxyborohydride (125 mg) and acetic acid (70 mg) were added to the reaction mixture. After stirring at ambient temperature for 3 hours, the mixture was

concentrated *in vacuo*, and the residue was partitioned between ethyl acetate and a saturated sodium bicarbonate solution. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was purified by a preparative thin layer chromatography developed with a mixture of chloroform, methanol and 28% ammonium hydroxide (100:10:1) to give 5-cyano-*N*-(3,4-dimethoxybenzyl)-2-[(*S*)-1-methylpyrrolidin-3-ylamino]benzamide (22 mg) as colorless crystals.

NMR (DMSO-d_6, δ): 1.51 (1H, m), 2.20-2.35 (2H, m), 2.25 (3H, s), 2.41 (1H, dd, J=4, 10Hz), 2.60-2.75 (2H, m), 3.72 (3H, s), 3.74 (3H, s), 4.05 (1H, m), 4.34 (2H, d, J=6Hz), 6.76 (1H, d, J=9Hz), 6.84 (1H, dd, J=2, 9Hz), 6.90 (1H, d, J=9Hz), 6.94 (1H, d, J=2Hz), 7.63 (1H, dd, J=2, 9Hz), 8.05 (1H, d, J=2Hz), 8.77 (1H, d, J=7Hz), 9.02 (1H, t, J=6Hz)

Example 20

(1) 2-[(*S*)-1-*tert*-Butoxycarbonylpyrrolidin-3-ylamino]-*N*-(3-chloro-4-methoxybenzyl)-5-trifluoromethylbenzamide (516 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-2-fluoro-5-trifluoromethylbenzamide (700 mg) and (*S*)-3-amino-1-*tert*-butoxycarbonylpyrrolidine (721 mg) in a similar manner to Example 12-(2) as an amorphous powder.

NMR (DMSO-d_6, δ): 1.39 (9H, s), 1.83 (1H, m), 2.20 (1H, m), 3.09 (1H, m), 3.25-3.45 (2H, m), 3.61 (1H, m), 3.83 (3H, s), 4.15 (1H, m), 4.36 (2H, d, J=6Hz), 6.93 (1H, d, J=8Hz), 7.10 (1H, d, J=8Hz), 7.25 (1H, dd, J=2, 8Hz), 7.36 (1H, d, J=2Hz), 7.59 (1H, brd, J=8Hz), 7.98 (1H, brs), 8.61 (1H, d, J=7Hz), 9.17 (1H, t, J=6Hz)

(2) To a solution of 2-[(*S*)-1-*tert*-butoxycarbonylpyrrolidin-3-ylamino]-*N*-(3-chloro-4-methoxybenzyl)-5-trifluoromethylbenzamide (430 mg) in chloroform (3 ml) was added trifluoroacetic acid (5 ml), and the mixture was stirred at 20°C for 2 hours. The mixture was concentrated *in vacuo* and the residue was partitioned between chloroform and a saturated sodium bicarbonate solution. The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to give *N*-(3-chloro-4-methoxybenzyl)-2-[(*S*)-pyrrolidin-3-ylamino]-5-trifluromethylbenzamide (262 mg) as an amorphous powder.

NMR (DMSO-d_6, δ): 1.49 (1H, m), 2.10 (1H, m), 2.55 (1H, dd, J=4, 10Hz),

2.7-2.95 (2H, m), 3.13 (1H, dd, J=6, 10Hz), 3.83 (3H, s), 3.93 (1H, m), 4.35 (2H, d, J=6Hz), 6.83 (1H, d, J=8Hz), 7.11 (1H, d, J=8Hz), 7.26 (1H, dd, J=2, 8Hz), 7.37 (1H, d, J=2Hz), 7.56 (1H, dd, J=2, 8Hz), 7.95 (1H, d, J=2Hz), 8.52 (1H, d, J=7Hz), 9.13 (1H, t, J=6Hz)

(3) A 4N solution of hydrogen chloride in ethyl acetate (0.5 ml) was added to a solution of *N*-(3-chloro-4-methoxybenzyl)-2-[(*S*)-pyrrolidin-3-ylamino]-5-trifluoromethylbenzamide (139 mg) in diethyl ether (2 ml). After stirred for 30 minutes, the mixture was concentrated *in vacuo*, and the residue was triturated with diethyl ether to give *N*-(3-chloro-4-methoxybenzyl)-2-[(*S*)-pyrrolidin-3-ylamino]-5-trifluoromethylbenzamide hydrochloride (143 mg) as an amorphous powder.
NMR (DMSO-d_6, δ): 1.38 (1H, m), 2.34 (1H, m), 3.05 (1H, dd, J=4, 10Hz), 3.15-3.45 (2H, m), 3.51 (1H, dd, J=7, 10Hz), 3.83 (3H, s), 4.30 (1H, m), 4.37 (2H, d, J=6Hz), 6.90 (1H, d, J=9Hz), 7.12 (1H, d, J=9Hz), 7.27 (1H, dd, J=2, 9Hz), 7.38 (1H, d, J=2Hz), 7.63 (1H, dd, J=2, 9Hz), 8.03 (1H, d, J=2Hz), 8.62 (1H, d, J=9Hz), 9.19 (1H, br), 9.25 (1H, t, J=6Hz)

Example 21

(1) A solution of methyl chloroformate (0.40 ml) in chloroform (5 ml) was added to a mixture of methyl (*S*)-3-amino-2-(benzyloxycarbonylamino)propionate hydrochloride (1 g) and triethylamine (1.45 ml) in chloroform (10 ml) with ice cooling. The mixture was stirred on an ice bath for 2 hours and concentrated *in vacuo*. The residue was partitioned between ethyl acetate and 3.6% hydrochloric acid, and the organic layer was washed with a saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography eluting with 5% methanol in chloroform to give methyl (*S*)-2-(benzyloxycarbonylamino)-3-methoxycarbonylamino)propionate (808 mg) as a white solid.
NMR ($CDCl_3$, δ): 3.50-3.70 (2H, m), 3.65 (3H, s), 3.77 (3H, s), 4.44 (1H, m), 5.00 (1H, m), 5.12 (2H, s), 5.75 (1H, m), 7.25-7.45 (5H, m)

(2) To a solution of methyl (*S*)-2-(benzyloxycarbonylamino)-3-(methoxycarbonylamino)propionate (781 mg) in methanol (8 ml) was

added sodium borohydride (190 mg) with ice cooling. The mixture was stirred for 1 hour at ambient temperature, then sodium borohydride (190 mg) was added thereto. The mixture was stirred for 1 hour at ambient temperature, quenched by 3.6% hydrochloric acid, and concentrated *in vacuo*. The residue was partitioned between ethyl acetate and a saturated sodium bicarbonate solution. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The crystalline residue was suspended in hot diisopropyl ether, cooled with stirring, collected and washed with diisopropyl ether to give (*S*)-2-(benzyloxycarbonylamino)-3-(methoxycarbonylamino)propanol (576 mg) as colorless crystals.
NMR ($CDCi_3$, δ): 3.20-3.80 (5H, m), 3.69 (3H, s), 5.00-5.15 (1H, m), 5.10 (2H, s), 5.35 (1H, m), 7.26-7.40 (5H, m)

(3) A mixture of (*S*)-2-(benzyloxycarbonylamino)-3-(methoxycarbonylamino)propanol (541 mg) and 10% palladium on activated carbon (60 mg) in methanol (10 ml) was hydrogenated under hydrogen atmosphere (3.5 atm) for 6 hours at between 30 and 35°C. The mixture was filtered through a celite pad and washed with methanol. The filtrate and the washings were combined and concentrated *in vacuo*. The residue was dissolved in ethyl acetate. The solution was dried over magnesium sulfate, and concentrated *in vacuo* to obtain (*S*)-2-amino-3-(methoxycarbonylamino)propanol (325 mg) as a white solid.
NMR ($CDCl_3$:CD_3OD=10:1, δ): 2.92 (1H, m), 3.10-3.30 (2H, m), 3.50 (2H, d, J=5Hz), 3.68 (3H, s)

(4) 5-Cyano-*N*-(3,4-dimethoxybenzyl)-2-[(*S*)-2-hydroxy-1-(methoxycarbonylaminomethyl)ethylamino]benzamide (173 mg) was prepared from 5-cyano-*N*-(3,4-dimethoxybenzyl)-2-fluorobenzamide (150 mg) and (*S*)-2-amino-3-(methoxycarbonylamino)propanol (142 mg) in a similar manner to Example 12-(2) as white crystals.
NMR (DMSO-d_6, δ): 2.95-3.20 (2H, m), 3.45-3.60 (2H, m), 3.53 (3H, s), 3.59 (1H, m), 3.72 (3H, s), 3.74 (3H, s), 4.35 (2H, d, J=6Hz), 4.95 (1H, t, J=5Hz), 6.84 (1H, dd, J=2, 9Hz), 6.90 (1H, d, J=9Hz), 6.94 (1H, d, J=2Hz), 7.04 (1H, d, J=9Hz), 7.36 (1H, t, J=5Hz), 7.62 (1H, dd, J=2, 9Hz), 8.03 (1H, d, J=2Hz), 8.81 (1H, d, J=7Hz), 8.97 (1H, t, J=6Hz)

Example 22

N-(3-Chloro-4-methoxybenzyl)-2-[(*S*)-2-hydroxy-1-(methoxycarbonyl-aminomethyl)ethylamino]-5-trifluoromethylbenzamide (107 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-2-fluoro-5-trifluoromethylbenzamide (150 mg) and (*S*)-2-amino-3-(methoxycarbonylamino)propanol (147 mg) in a similar manner to Example 12-(2) as an amorphous powder.

NMR (DMSO-d_6, δ): 3.00-3.20 (2H, m), 3.30-3.70 (3H, m), 3.53 (3H, s), 3.83 (3H, s), 4.36 (2H, d, J=6Hz), 4.91 (1H, t, J=4Hz), 7.07 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.26 (1H, dd, J=2, 9Hz), 7.34 (1H, t, J=6Hz), 7.37 (1H, d, J=2Hz), 7.54 (1H, brd, J=9Hz), 7.93 (1H, brs), 8.61 (1H, d, J=7Hz), 9.08 (1H, t, J=6Hz)

Example 23

(1) 2-[(*S*)-1-(*tert*-Butoxycarbonylaminomethyl)-2-hydroxyethylamino]-5-cyano-*N*-(3,4-dimethoxybenzyl)-benzamide (1.23 g) was prepared from 5-cyano-*N*-(3,4-dimethoxybenzyl)-2-fluorobenzamide (1 g) and (*S*)-2-amino-3-(*tert*-butoxycarbonylamino)propanol (1.21 g) in a similar manner to Example 12-(2) as white crystals.

NMR (DMSO-d_6, δ): 1.36 (9H, s), 3.00-3.10 (2H, m), 3.45-3.55 (2H, m), 3.60 (1H, m), 3.72 (3H, s), 3.74 (3H, s), 4.33 (2H, d, J=6Hz), 4.91 (1H, t, J=4Hz), 6.83 (1H, d, J=9Hz), 6.90 (1H, d, J=9Hz), 6.94 (1H, s), 6.95-7.05 (2H, m), 7.61 (1H, d, J=9Hz), 8.03 (1H, s), 8.81 (1H, d, J=7Hz), 8.96 (1H, t, J=6Hz)

(2) A mixture of 2-[(*S*)-1-(*tert*-butoxycarbonylaminomethyl)-2-hydroxyethylamino]-5-cyano-*N*-(3,4-dimethoxybenzyl)benzamide (1.13 g) and a 4N solution of hydrogen chloride in ethyl acetate (10 ml) was stirred for 2 hours at ambient temperature. The mixture was diluted with diethyl ether and the precipitates were collected and washed with diethyl ether to obtain 2-[(*S*)-1-(aminomethyl)-2-hydroxyethylamino]-5-cyano-*N*-(3,4-dimethoxybenzyl)benzamide hydrochloride (1.06 g) as pale yellow crystals.

NMR (DMSO-d_6, δ): 2.88 (1H, m), 3.06 (1H, m), 3.51 (1H, dd, J=6, 10Hz), 3.64 (1H, dd, J=4, 10Hz), 3.73 (3H, s), 3.74 (3H, s), 3.90 (1H, m), 4.34-4.45 (2H, m), 5.23 (1H, m), 6.85 (1H, dd, J=2, 9Hz), 6.90 (1H, d, J=9Hz), 6.95 (1H, d, J=2Hz), 7.01 (1H, d, J=9Hz), 7.68 (1H, dd, J=2, 9Hz), 8.00

(2H, brs), 8.00 (1H, d, J=2Hz), 8.10 (1H, d, J=3Hz), 8.82 (1H, d, J=7Hz), 9.06 (1H, t, J=5Hz)

(3) 2-[(*S*)-1-(Aminomethyl)-2-hydroxyethylamino]-5-cyano-*N*-(3,4-dimethoxybenzyl)benzamide hydrochloride (480 mg) was partitioned between 10% methanol in chloroform and a saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with 10% methanol in chloroform 4 times. The combined extracts were dried over magnesium sulfate, and concentrated *in vacuo* to give 2-[(*S*)-1-(aminomethyl)-2-hydroxyethylamino]-5-cyano-*N*-(3,4-dimethoxybenzyl)benzamide (393 mg) as an amorphous powder.
NMR (DMSO-d_6, δ): 2.60-2.75 (2H, m), 3.40-3.65 (3H, m), 3.72 (3H, s), 3.74 (3H, s), 4.35 (2H, d, J=6Hz), 6.84 (1H, dd, J=2, 9Hz), 6.88 (1H, d, J=9Hz), 6.90 (1H, d, J=9Hz), 6.94 (1H, d, J=2Hz), 7.58 (1H, dd, J=2, 9Hz), 8.01 (1H, d, J=2Hz), 8.78 (1H, d, J=7Hz), 8.95 (1H, t, J=6Hz)

(4) A solution of 2-[(*S*)-1-(aminomethyl)-2-hydroxyethylamino]-5-cyano-*N*-(3,4-dimethoxybenzyl)benzamide (130 mg) in ethyl formate (3 ml) was refluxed overnight. After evaporation of the solvent, the residue was purified by a preparative thin layer chromatography on silica gel developed with 5% methanol in chloroform. The obtained product was triturated with diethyl ether to give 5-cyano-*N*-(3,4-dimethoxybenzyl)-2-[(*S*)-1-(formamidomethyl)-2-hydroxyethylamino]benzamide (110 mg) as an amorphous powder.
NMR (DMSO-d_6, δ): 3.10-3.40 (2H, m), 3.40-3.60 (2H, m), 3.64 (1H, m), 3.72 (3H, s), 3.74 (3H, s), 4.34 (2H, d, J=6Hz), 5.00 (1H, t, J=4Hz), 6.84 (1H, dd, J=2, 9Hz), 6.90 (1H, d, J=9Hz), 6.94 (1H, d, J=2Hz), 7.03 (1H, d, J=9Hz), 7.63 (1H, dd, J=2, 9Hz), 8.04 (1H, d, J=2Hz), 8.04 (1H, s), 8.21 (1H, t, J=6Hz), 8.82 (1H, d, J=7Hz), 8.97 (1H, t, J=6Hz)

Example 24

(1) 2-[(*S*)-1-(*tert*-Butoxycarbonylaminomethyl)-2-hydroxyethylamino]-*N*-(3-chloro-4-methoxybenzyl)-5-trifluoromethylbenzamide (856 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-2-fluoro-5-trifluoromethylbenzamide (1.00 g) and (*S*)-2-amino-3-(*tert*-butoxycarbonylamino)-propanol (1.05 g) in a similar manner to Example 12-(2) as an amorphous powder.

NMR (DMSO-d_6, δ): 1.36 (9H, s), 3.00-3.10 (2H, m), 3.45-3.65 (3H, m), 3.83 (3H, s), 4.34 (2H, d, J=6Hz), 4.87 (1H, t, J=4Hz), 6.90-7.05 (2H, m), 7.11 (1H, d, J=9Hz), 7.26 (1H, dd, J=2, 9Hz), 7.36 (1H, d, J=2Hz), 7.52 (1H, dd, J=2, 9Hz), 7.93 (1H, d, J=2Hz), 8.61 (1H, d, J=7Hz), 9.06 (1H, t, J=6Hz)

(2) 2-[(*S*)-1-(Aminomethyl)-2-hydroxyethylamino]-*N*-(3-chloro-4-methoxybenzyl)-5-trifluoromethylbenzamide (568 mg) was prepared from (*S*)-2-[1-(*tert*-butoxycarbonylaminomethyl)-2-hydroxyethylamino]-*N*-(3-chloro-4-methoxybenzyl)-5-trifluoromethylbenzamide (737 mg) in a similar manner to Examples 23-(2) and 23-(3) as an amorphous powder.
NMR (DMSO-d_6, δ): 2.65-2.80 (2H, m), 3.35-3.65 (3H, m), 3.83 (3H, s), 4.36 (2H, d, J=6Hz), 6.92 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.26 (1H, dd, J=2, 9Hz), 7.37 (1H, d, J=2Hz), 7.52 (1H, dd, J=2, 9Hz), 7.92 (1H, d, J=2Hz), 8.58 (1H, d, J=7Hz), 9.07 (1H, t, J=6Hz)

(3) To a solution of 2-[(*S*)-1-(aminomethyl)-2-hydroxyethylamino]-*N*-(3-chloro-4-methoxybenzyl)-5-trifluoromethylbenzamide (119 mg) in diethyl ether was added a 4N solution of hydrogen chloride in ethyl acetate (0.5 ml). After stirring for 30 minutes at ambient temperature, the mixture was concentrated *in vacuo* and the residue was triturated with n-hexane to obtain 2-[(*S*)-1-(aminomethyl)-2-hydroxyethylamino]-*N*-(3-chloro-4-methoxybenzyl)-5-trifluoromethylbenzamide hydrochloride (77 mg) as an amorphous powder.
NMR (DMSO-d_6, δ): 2.89 (1H, dd, J=6, 10Hz), 3.08 (1H, dd, J=5, 10Hz), 3.50 (1H, m), 3.63 (1H, m), 3.83 (3H, s), 3.37 (1H, m), 4.37 (2H, d, J=5Hz), 5.23 (1H, m), 7.04 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.26 (1H, dd, J=2, 9Hz), 7.38 (1H, d, J=2Hz), 7.59 (1H, dd, J=2, 9Hz), 7.98 (2H, brs), 8.00 (1H, d, J=2Hz), 8.63 (1H, d, J=7Hz), 9.18 (1H, t, J=5Hz)

Example 25

N-(3-Chloro-4-methoxybenzyl)-2-[(*S*)-1-(formamidomethyl)-2-hydroxyethylamino]-5-trifluoromethylbenzamide (72 mg) was prepared from 2-[(*S*)-1-(aminomethyl)-2-hydroxyethylamino]-*N*-(3-chloro-4-methoxybenzyl)-5-trifluoromethylbenzamide (130 mg) in a similar manner to Example 23-(4) as an amorphous powder.
NMR (DMSO-d_6, δ): 3.10-3.40 (2H, m), 3.40-3.60 (2H, m), 3.62 (1H, m),

3.83 (3H, s), 4.35 (2H, d, J=6Hz), 4.96 (1H, t, J=4Hz), 7.06 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.26 (1H, dd, J=2, 9Hz), 7.37 (1H, d, J=2Hz), 7.54 (1H, brd, J=9Hz), 7.94 (1H, s), 8.05 (1H, brs), 8.20 (1H, t, J=6Hz), 8.64 (1H, d, J=7Hz), 9.09 (1H, t, J=6Hz)

Example 26

(1) *N*-(3-Chloro-4-methoxybenzyl)-5-cyano-2-fluorobenzamide (36.7 g) was prepared from 5-cyano-2-fluorobenzoic acid (20 g) and 3-chloro-4-methoxybenzylamine (21.2 g) in a similar manner to Example 1-(3).
NMR (DMSO-d_6, δ): 3.84 (3H, s), 4.40 (2H, d, J=6Hz), 7.12 (1H, d, J=9Hz), 7.29 (1H, dd, J=2, 9Hz), 7.40 (1H, d, J=4Hz), 7.57 (1H, t, J=9Hz), 8.06 (1H, m), 8.13 (1H, dd, J=2, 6Hz), 9.07 (1H, t, J=6Hz)

(2) *N*-(3-Chloro-4-methoxybenzyl)-5-cyano-2-[(*S*)-1-(carbamoyl)ethylamino]benzamide (65 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-5-cyano-2-fluorobenzamide (117 mg) and L-alaninamide hydrochloride (92 mg) in a similar manner to Example 15-(6).
NMR (DMSO-d_6, δ): 1.34 (3H, d, J=7Hz), 3.83 (3H, s), 4.04 (1H, m), 4.36 (2H, d, J=6Hz), 6.61 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.19 (1H, brs), 7.28 (1H, dd, J=2, 9Hz), 7.39 (1H, d, J=2Hz), 7.60 (1H, brs), 7.66 (1H, dd, J=2, 9Hz), 8.08 (1H, d, J=2Hz), 8.92 (1H, d, J=8Hz), 9.06 (1H, t, J=6Hz)

Example 27

N-(3-Chloro-4-methoxybenzyl)-5-cyano-2-[(1*R*,2*R*)-2-hydroxy-1-(hydroxymethyl)propylamino]benzamide (99 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-5-cyano-2-fluorobenzamide (105 mg) and L-threoninol (104 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 1.05 (3H, d, J=7Hz), 3.30-3.55 (3H, m), 3.83 (3H, s), 4.00 (1H, m), 4.35 (2H, d, J=6Hz), 4.77 (1H, t, J=5Hz), 4.89 (1H, d, J=4Hz), 6.87 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.28 (1H, dd, J=2, 9Hz), 7.37 (1H, d, J=2Hz), 7.58 (1H, dd, J=2, 9Hz), 8.01 (1H, d, J=2Hz), 8.83 (1H, d, J=8Hz), 9.00 (1H, t, J=6Hz)

Example 28

5-Cyano-2-(*t*-2,*t*-3-dihydroxy-*r*-1-cyclopentylamino)-*N*-(3,4-dimethoxybenzyl)benzamide (104 mg) was prepared from 5-cyano-2-fluoro-*N*-(3,4-dimethoxybenzyl)benzamide (125 mg) and *t*-3-amino-*r*-

1,c-2-cyclopentanediol (98 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 1.24 (1H, m), 1.59 (1H, m), 1.88 (1H, m), 2.27 (1H, m), 3.62 (1H, m), 3.72 (1H, m), 3.74 (3H, s), 3.76 (3H, s), 3.89 (1H, m), 4.57 (1H, d, J=5Hz), 4.79 (1H, d, J=5Hz), 4.86 (1H, d, J=5Hz), 6.81-6.96 (4H, m), 7.63 (1H, dd, J=2, 9Hz), 8.07 (1H, d, J=2Hz), 8.76 (1H, d, J=8Hz), 9.04 (1H, t, J=6Hz)

Example 29

(1) To a solution of 3-cyclohexene-1-carboxylic acid (1.8 g) in benzene (40 ml) were added triethylamine (2.2 ml) and diphenylphosphoryl azide (3.93 g). After the mixture was refluxed for 2 hours, benzyl alcohol (1.54 g) was added, and the mixture was refluxed for additional 10 hours. The resulting mixture was evaporated *in vacuo*, diluted with ethyl acetate and washed with 1*N*-hydrochloric acid, sodium hydrogen carbonate solution and brine successively. The organic layer was dried over sodium sulfate and evaporated *in vacuo*. The residue was recrystallized from a mixture of n-hexane and diethyl ether to give benzyl *N*-(3-cyclohexen-1-yl)carbamate (1.72 g) as a solid.
NMR ($CDCl_3$, δ): 1.58 (1H, m), 1.82-1.95 (2H, m), 2.05-2.36 (2H, m), 2.40 (1H, m), 3.88 (1H, m), 4.78 (1H, m), 5.55-5.72 (2H, m), 7.27-7.39 (5H, m)

(2) To a solution of benzyl *N*-(3-cyclohexen-1-yl)carbamate (1.7 g) in a mixture of tetrahydrofuran (40 ml) and water (2 ml) were added *N*-methylmorpholine *N*-oxide (1.29 g) and 4% aqueous solution of osmium tetroxide (5 ml), and the mixture was stirred for 30 minutes at ambient temperature. The resulting mixture was evaporated *in vacuo*, diluted with ethyl acetate and washed with 1*N*-hydrochloric acid, a sodium bicarbonate solution and brine successively. The organic layer was dried over sodium sulfate and evaporated *in vacuo*. The residue was recrystallized from ethyl acetate to give benzyl *N*-(*t*-3,*t*-4-dihydroxy-*r*-1-cyclohexyl)-carbamate (374 mg) as a solid.
NMR (DMSO-d_6, δ): 1.15 (1H, m), 1.34 (1H, m), 1.44-1.83 (4H, m), 3.35 (1H, m), 3.64 (1H, m), 3.74 (1H, m), 4.28 (1H, d, J=3Hz), 4.34 (1H, d, J=5Hz), 4.99 (2H, s), 7.08 (1H, d, J=7Hz), 7.26-7.41 (5H, m)

The mother liquors was chromatographed on silica gel eluting with 10% methanol in chloroform to give benzyl *N*-(*c*-3,*c*-4-dihydroxy-*r*-1-

cyclohexyl)carbamat (565 mg) as a solid.
NMR (DMSO-d_6, δ): 1.24-1.69 (6H, m), 3.23-3.46 (2H, m), 3.63 (1H, m), 4.20 (1H, d, J=2Hz), 4.50 (1H, d, J=5Hz), 4.99 (2H, s), 7.17 (1H, d, J=7Hz), 7.26-7.42 (5H, m)

(3) To a solution of benzyl *N*-(*t*-3,*t*-4-dihydroxy-*r*-1-cyclohexyl)carbamate (173 mg) in ethanol (6 ml) was added 10% palladium on activated carbon (34 mg), and the mixture was stirred under hydrogen atmosphere (3 atm) at ambient temperature for 1 hour. The catalyst was removed by filtration, and the filtrate was evaporated *in vacuo*. The residue was recrystallized from a mixture of ethanol and diethyl ether to give *t*-4-amino-*r*-1,*c*-2-cyclohexanediol (73 mg) as a solid.
NMR ($CDCl_3$, δ): 1.06-1.44 (2H, m), 1.65-1.66 (2H, m), 1.84 (1H, m), 2.04 (1H, m), 3.07 (1H, m), 3.58 (1H, m), 3.96 (1H, m)

(4) *N*-(3-Chloro-4-methoxybenzyl)-5-cyano-2-(*t*-3,*t*-4-dihydroxy-*r*-1-cyclohexylamino)benzamide (92 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-5-cyano-2-fluorobenzamide (85 mg) and *t*-4-amino-*r*-1,*c*-2-cyclohexanediol (70 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 1.26 (1H, m), 1.41 (1H, m), 1.53 (1H, m), 1.71 (1H, m), 1.82-2.02 (2H, m), 3.52 (1H, m), 3.66-3.80 (2H, m), 3.83 (3H, s), 4.34 (2H, d, J=5Hz), 4.44 (1H, d, J=5Hz), 4.49 (1H, d, J=3Hz), 6.79 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.26 (1H, dd, J=2, 9Hz), 7.37 (1H, d, J=2Hz), 7.63 (1H, dd, J=2, 9Hz), 8.05 (1H, d, J=2Hz), 8.65 (1H, d, J=8Hz), 9.05 (1H, t, J=5Hz)

Example 30

5-Cyano-2-[(1*S*,2*S*)-2-hydroxycyclopentylamino]-*N*-(3,4-dimethoxybenzyl)benzamide (104 mg) was prepared from 5-cyano-2-fluoro-*N*-(3,4-dimethoxybenzyl)benzamide (110 mg) and (1*S*,2*S*)-2-aminocyclopentanol (189 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 1.38 (1H, m), 1.46-1.85 (4H, m), 2.18 (1H, m), 3.58 (1H, m), 3.72 (3H, s), 3.74 (3H, s), 3.84 (1H, m), 4.35 (1H, d, J=6Hz), 5.00 (1H, d, J=4Hz), 6.81-6.96 (4H, m), 7.64 (1H, dd, J=2, 9Hz), 8.06 (1H, d, J=2Hz), 8.69 (1H, d, J=6Hz), 9.02 (1H, t, J=6Hz)

Example 31

N-(3-Chloro-4-methoxybenzyl)-5-cyano-2-[(1*S*,2*S*)-2-hydroxycyclopentylamino]benzamide (103 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-5-cyano-2-fluorobenzamide (107 mg) and (1*S*,2*S*)-2-aminocyclopentanol (181 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 1.38 (1H, m), 1.46-1.85 (4H, m), 2.18 (1H, m), 3.59 (1H, m), 3.83 (3H, s), 3.84 (1H, m), 4.35 (1H, d, J=6Hz), 5.00 (1H, d, J=5Hz), 6.94 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.26 (1H, dd, J=2, 9Hz), 7.37 (1H, d, J=2Hz), 7.64 (1H, dd, J=2, 9Hz), 8.06 (1H, d, J=2Hz), 8.68 (1H, d, J=6Hz), 9.06 (1H, t, J=6Hz)

Example 32

(1) *c*-4-Amino-*r*-1,*c*-2-cyclohexanediol (254 mg) was prepared from benzyl *N*-(*c*-3,*c*-4-dihydroxy-*r*-1-cyclohexyl)carbamate (540 mg) in a similar manner to Example 29-(3).
NMR ($CDCl_3$, δ): 1.42-1.78 (7H, m), 1.91 (1H, m), 2.88 (1H, m), 3.68 (1H, m), 3.75 (1H, m)

(2) *N*-(3-Chloro-4-methoxybenzyl)-5-cyano-2-(*c*-3,*c*-4-dihydroxy-*r*-1-cyclohexylamino)benzamide (72 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-5-cyano-2-fluorobenzamide (88 mg) and *c*-4-amino-*r*-1,*c*-2-cyclohexanediol (72 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 1.38-1.84 (6H, m), 3.43-3.59 (2H, m), 3.68 (1H, m), 3.83 (3H, s), 4.28-4.38 (3H, m), 4.53 (1H, d, J=5Hz), 6.86 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.27 (1H, dd, J=2, 9Hz), 7.37 (1H, d, J=2Hz), 7.60 (1H, dd, J=2, 9Hz), 8.03 (1H, d, J=2Hz), 8.67 (1H, d, J=7Hz), 9.02 (1H, t, J=5Hz)

Example 33

5-Cyano-2-(*c*-3,*c*-4-dihydroxy-*r*-1-cyclohexylamino)-*N*-(3,4-dimethoxybenzyl)benzamide (73 mg) was prepared from 5-cyano-2-fluoro-*N*-(3,4-dimethoxybenzyl)benzamide (91 mg) and *c*-4-amino-*r*-1,*c*-2-cyclohexanediol (69 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 1.38-1.84 (6H, m), 3.44-3.59 (2H, m), 3.68 (1H, m), 3.72 (3H, s), 3.74 (3H, s), 4.31-4.37 (3H, m), 4.54 (1H, d, J=5Hz), 6.81-6.96 (4H, m), 7.59 (1H, dd, J=2, 9Hz), 8.09 (1H, d, J=2Hz), 8.66 (1H, d, J=8Hz), 8.98 (1H, t, J=6Hz)

Example 34

(1) To a solution of *r*-1,*c*-3,*c*-5-cyclohexanetriol dihydrate (147 mg; water was removed by azeotropic distillation with ethanol-toluene) in pyridine (2 ml) was added *p*-toluenesulfonyl chloride (1.36 g), and the mixture was stirred for 40 minutes at ambient temperature. The resulting mixture was evaporated *in vacuo*, diluted with ethyl acetate and washed with water and brine successively. The organic layer was dried over sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with 10% methanol in chloroform to give *c*-5-tosyloxy-*r*-1,*c*-3-cyclohexanediol (140 mg) as a solid.
NMR ($CDCl_3$+D_2O, δ): 1.42 (1H, m), 1.52-1.67 (2H, m), 2.08-2.23 (3H, m), 2.46 (3H, s), 3.63-3.76 (2H, m), 4.48 (1H, m), 7.34 (2H, d, J=8Hz), 7.79 (2H, d, J=8Hz)

(2) Sodium azide (76 mg) was added to a solution of *c*-5-tosyloxy-*r*-1,*c*-3-cyclohexanediol (140 mg) in a mixture of dimethylformamide (1.5 ml) and water (0.2 ml). After stirring for 2 hours at 80°C, the mixture was diluted with ethyl acetate. The solution was washed with water and brine successively, dried over sodium sulfate and evaporated *in vacuo*. The residue was triturated with diethyl ether to give *t*-5-azido-*r*-1,*c*-3-cyclohexanediol (26 mg).
NMR ($CDCl_3$, δ): 1.55-1.80 (3H, m), 1.94 (1H, m), 2.04-2.16 (2H, m), 2.58 (2H, d, J=6Hz), 4.08 (1H, m), 4.16-4.29 (2H, m)

(3) *t*-5-Amino-*r*-1,*c*-3-cyclohexanediol (175 mg) was prepared from *t*-5-azido-*r*-1,*c*-3-cyclohexanediol (210 mg) in a similar manner to Example 29-(3).
NMR ($CDCl_3$:CD_3OD=1:1, δ): 1.31 (2H, m), 1.55 (1H, dt, J=8, 2Hz), 1.95-2.10 (3H, m), 3.41 (1H, m), 4.19 (2H, m)

(4) 5-Cyano-2-(*t*-3,*t*-5-dihydroxy-*r*-1-cyclohexylamino)-*N*-(3,4-dimethoxybenzyl)benzamide (84 mg) was prepared from 5-cyano-2-fluoro-*N*-(3,4-dimethoxybenzyl)benzamide (108 mg) and *t*-5-amino-*r*-1,*c*-3-cyclohexanediol (81 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 1.21 (1H, m), 1.41 (2H, m), 1.85 (2H, m), 2.04 (1H, m), 3.59-3.73 (2H, m), 3.73 (3H, s), 3.74 (3H, s), 4.04 (1H, m), 4.36 (1H, d,

J=5Hz), 4.75 (1H, d, J=5Hz), 6.79-6.96 (4H, m), 7.63 (1H, dd, J=2, 9Hz), 8.08 (1H, d, J=2Hz), 8.88 (1H, d, J=8Hz), 9.04 (1H, t, J=6Hz)

Example 35

N-(3-Chloro-4-methoxybenzyl)-5-cyano-2-(*t*-3,*t*-5-dihydroxy-*r*-1-cyclohexylamino)benzamide (149 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-5-cyano-2-fluorobenzamide (122 mg) and *t*-5-amino-*r*-1,*c*-3-cyclohexanediol (90 mg) in a similar manner to Example 12-(2). NMR (DMSO-d_6, δ): 1.20 (1H, m), 1.41 (2H, m), 1.85 (2H, m), 2.03 (1H, m), 3.59-3.73 (2H, m), 3.83 (3H, s), 4.03 (1H, m), 4.37 (2H, d, J=5Hz), 4.74 (2H, d, J=5Hz), 6.84 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.27 (1H, dd, J=2, 9Hz), 7.37 (1H, d, J=2Hz), 7.64 (1H, dd, J=2, 9Hz), 8.09 (1H, d, J=2Hz), 8.87 (1H, d, J=7Hz), 9.08 (1H, t, J=5Hz)

Example 36

N-(3-Chloro-4-methoxybenzyl)-5-cyano-2-(*t*-3,*t*-4-dihydroxy-*r*-1-cyclopentylamino)benzamide (138 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-5-cyano-2-fluorobenzamide (125 mg) and *t*-4-amino-*r*-1,*c*-2-cyclopentanediol (69 mg) in a similar manner to Example 12-(2). NMR (DMSO-d_6, δ): 1.56 (2H, m), 2.10 (2H, m), 3.83 (3H, s), 3.93-4.09 (3H, m), 4.34 (2H, d, J=6Hz), 4.54 (1H, d, J=5Hz), 6.71 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.26 (1H, dd, J=2, 9Hz), 7.37 (1H, d, J=2Hz), 7.63 (1H, dd, J=2, 9Hz), 8.06 (1H, d, J=2Hz), 8.68 (1H, d, J=6Hz), 9.06 (1H, t, J=6Hz)

Example 37

5-Cyano-2-(*t*-3,*t*-4-dihydroxy-*r*-1-cyclohexylamino)-*N*-(3,4-dimethoxybenzyl)benzamide (203 mg) was prepared from 5-cyano-2-fluoro-*N*-(3,4-dimethoxybenzyl)benzamide (160 mg) and *t*-4-amino-*r*-1,*c*-2-cyclohexanediol (100 mg) in a similar manner to Example 12-(2). NMR (DMSO-d_6, δ): 1.26 (1H, m), 1.41 (1H, m), 1.53 (1H, m), 1.71 (1H, m), 1.82-2.02 (2H, m), 3.52 (1H, m), 3.66-3.80 (2H, m), 3.72 (3H, s), 3.74 (3H, s), 4.34 (2H, d, J=6Hz), 4.44 (1H, d, J=5Hz), 4.50 (1H, d, J=4Hz), 6.76-6.94 (4H, m), 7.62 (1H, dd, J=2, 9Hz), 8.05 (1H, d, J=2Hz), 8.66 (1H, d, J=8Hz), 9.01 (1H, t, J=6Hz)

Example 38

To a solution of *N*-(3-chloro-4-methoxybenzyl)-5-cyano-2-(*t*-3,*t*-4-dihydroxy-*r*-1-cyclopentylamino)benzamide (88 mg) in 1,2-dichloroethane (5 ml) were added 2,6-di-*tert*-butyl-4-methylphenol (121 mg) and trimethyloxonium tetrafluoroborate (75 mg), and the mixture was refluxed for 3 hours. The resulting mixture was diluted with ethyl acetate and washed with an aqueous sodium bicarbonate and brine successively. The organic layer was dried over sodium sulfate, evaporated *in vacuo* and chromatographed on silica gel eluting with a mixture of n-hexane and ethyl acetate (2:1) to give *N*-(3-chloro-4-methoxybenzyl)-5-cyano-2-(*t*-3,*t*-4-dimethoxy-*r*-1-cyclopentylamino)-benzamide (24 mg) as a solid.

NMR (DMSO-d_6, δ): 1.57 (2H, m), 2.24 (2H, m), 3.27 (6H, s), 3.83 (3H, s), 3.80-3.87 (2H, m), 3.97 (1H, m), 4.35 (2H, d, J=6Hz), 6.74 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.26 (1H, dd, J=2, 9Hz), 7.37 (1H, d, J=2Hz), 7.63 (1H, dd, J=2, 9Hz), 8.07 (1H, d, J=2Hz), 8.69 (1H, d, J=6Hz), 9.08 (1H, t, J=6Hz)

Example 39

5-Cyano-*N*-(3,4-dimethoxybenzyl)-2-(*t*-3,*t*-4-dimethoxy-*r*-1-cyclohexylamino)benzamide (20 mg) was prepared from 5-cyano-2-(*t*-3,*t*-4-dihydroxy-*r*-1-cyclohexylamino)-*N*-(3,4-dimethoxybenzyl)benzamide (96 mg) in a similar manner to Example 38.

NMR (DMSO-d_6, δ): 1.26 (1H, m), 1.39 (1H, m), 1.59-1.80 (2H, m), 1.93 (1H, m), 2.14 (1H, m), 3.26 (3H, s), 3.33 (1H, m), 3.34 (3H, s), 3.59-3.68 (2H, m), 3.72 (3H, s), 3.74 (3H, s), 4.34 (2H, d, J=6Hz), 6.74-6.94 (4H, m), 7.62 (1H, dd, J=2, 9Hz), 8.05 (1H, d, J=2Hz), 8.67 (1H, d, J=8Hz), 9.02 (1H, t, J=6Hz)

Example 40

(1) 5-Cyano-2-(*t*-3,*t*-4-dihydroxy-*r*-1-cyclopentylamino)-*N*-(3,4-dimethoxybenzyl)benzamide (140 mg) was prepared from 5-cyano-2-fluoro-*N*-(3,4-dimethoxybenzyl)benzamide (128 mg) and *t*-4-amino-*r*-1,*c*-2-cyclopentanediol (62 mg) in a similar manner to Example 12-(2).

NMR (DMSO-d_6, δ): 1.56 (2H, m), 2.10 (2H, m), 3.72 (3H, s), 3.74 (3H, s), 3.93-4.06 (3H, m), 4.34 (2H, d, J=6Hz), 4.54 (2H, d, J=4Hz), 6.70 (1H, d, J=9Hz), 6.83 (1H, dd, J=2, 8Hz), 6.88-6.94 (2H, m), 7.63 (1H, dd, J=2, 9Hz), 8.05 (1H, d, J=2Hz), 8.67 (1H, d, J=7Hz), 9.02 (1H, t, J=6Hz)

(2) To a solution of 5-cyano-2-(*t*-3,*t*-4-dihydroxy-*r*-1-cyclopentylamino)-*N*-(3,4-dimethoxybenzyl)benzamide (30 mg) in tetrahydrofuran (5 ml) was added 1,1'-carbonyldiimidazole (19 mg), and the mixture was refluxed for 3 hours. The resulting mixture was diluted with ethyl acetate and washed with 1*N*-hydrochloric acid, an aqueous sodium bicarbonate solution and brine successively. The organic layer was dried over sodium sulfate, evaporated *in vacuo* and triturated with a mixture of ethyl acetate and diethyl ether to give 5-cyano-2-(*t*-3,*t*-4-carbonyldioxy-*r*-1-cyclopentylamino)-*N*-(3,4-dimethoxybenzyl)benzamide (27 mg) as a solid.
NMR (DMSO-d_6, δ): 1.75 (2H, m), 2.46 (2H, m), 3.72 (3H, s), 3.74 (3H, s), 4.22 (1H, m), 4.35 (2H, d, J=6Hz), 5.24 (2H, m), 6.83 (1H, dd, J=2, 8Hz), 6.88-6.94 (2H, m), 7.09 (1H, d, J=9Hz), 7.64 (1H, dd, J=2, 9Hz), 8.07 (1H, d, J=2Hz), 8.73 (1H, d, J=7Hz), 9.05 (1H, t, J=6Hz)

Example 41

5-Cyano-*N*-(3,4-dimethoxybenzyl)-2-(*t*-3,*t*-5-dimethoxy-*r*-1-cyclohexylamino)benzamide (15 mg) was prepared from 5-cyano-2-(*t*-3,*t*-5-dihydroxy-*r*-1-cyclohexylamino)-*N*-(3,4-dimethoxybenzyl)benzamide (65 mg) in a similar manner to Example 38.
NMR (DMSO-d_6, δ): 1.23 (1H, m), 1.53 (2H, m), 1.94 (2H, m), 2.31 (1H, m), 3.22 (6H, s), 3.34 (2H, m), 3.72 (3H, s), 3.75 (3H, s), 4.05 (1H, m), 4.37 (1H, d, J=6Hz), 6.80-6.97 (4H, m), 7.64 (1H, dd, J=2, 9Hz), 8.08 (1H, d, J=2Hz), 8.84 (1H, d, J=8Hz), 9.05 (1H, t, J=6Hz)

Example 42

N-(3-Chloro-4-methoxybenzyl)-2-(*t*-3,*t*-5-dihydroxy-*r*-1-cyclohexylamino)-5-trifluoromethylbenzamide (56 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-2-fluoro-5-trifluoromethylbenzamide (156 mg) and *t*-5-amino-*r*-1,*c*-3-cyclohexanediol (74 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 1.20 (1H, m), 1.40 (2H, m), 1.86 (2H, m), 2.05 (1H, m), 3.66 (2H, m), 3.83 (3H, s), 4.02 (1H, m), 4.37 (2H, d, J=5Hz), 4.72 (2H, d, J=5Hz), 6.87 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.25 (1H, dd, J=2, 9Hz), 7.37 (1H, d, J=2Hz), 7.66 (1H, dd, J=2, 9Hz), 7.97 (1H, d, J=2Hz), 8.65 (1H, d, J=7Hz), 9.14 (1H, t, J=5Hz)

Example 43

(1) *r*-1,*c*-3-Dimethoxy-*c*-5-tosyloxycyclohexane (26 mg) was prepared from *c*-5-tosyloxy-*r*-1,*c*-3-cyclohexanediol (140 mg) in a similar manner to Example 38.
NMR ($CDCl_3$, δ): 1.07 (1H, q, J=12Hz), 1.38 (2H, q, J=12Hz), 2.28-2.46 (3H, m), 2.45 (3H, s), 3.09 (2H, m), 3.31 (6H, s), 4.40 (1H, m), 7.35 (2H, d, J=8Hz), 7.80 (2H, d, J=8Hz)

(2) *t*-5-Azido-*r*-1,*c*-3-dimethoxycyclohexane (345 mg) was prepared from *r*-1,*c*-3-dimethoxy-*c*-5-tosyloxycyclohexane (470 mg) and sodium azide (263 mg) in a similar manner to Example 34-(2).
NMR ($CDCl_3$, δ): 1.23 (1H, q, J=12Hz), 1.48 (2H, m), 2.07-2.17 (2H, m), 2.41 (1H, m), 3.37 (6H, s), 3.45 (2H, m), 4.11 (1H, m)

(3) *t*-5-Amino-*r*-1,*c*-3-dimethoxycyclohexane (230 mg) was prepared from *t*-5-azido-*r*-1,*c*-3-dimethoxycyclohexane (340 mg) in a similar manner to Example 29-(3).
NMR ($CDCl_3$, δ): 1.30 (1H, m), 1.51 (2H, m), 1.81 (2H, m), 2.33 (1H, m), 3.36 (6H, s), 3.51 (1H, m), 3.61 (2H, m)

(4) *N*-(3-Chloro-4-methoxybenzyl)-5-cyano-2-(*t*-3,*t*-5-dimethoxy-*r*-1-cyclohexylamino)benzamide (118 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-5-cyano-2-fluorobenzamide (110 mg) and *t*-5-amino-*r*-1,*c*-3-dimethoxycyclohexane (71 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 1.23 (1H, m), 1.52 (2H, m), 1.94 (2H, m), 2.31 (1H, m), 3.21 (6H, s), 3.33 (2H, m), 3.83 (3H, s), 4.05 (1H, m), 4.37 (2H, d, J=6Hz), 6.83 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.27 (1H, dd, J=2, 9Hz), 7.39 (1H, d, J=2Hz), 7.65 (1H, dd, J=2, 9Hz), 8.08 (1H, d, J=2Hz), 8.77 (1H, d, J=7Hz), 9.09 (1H, t, J=6Hz)

Example 44

(1) To a solution of (1*R*,4*S*)-1-acetoxy-4-(*tert*-butyldimethylsilyloxy)-2-cyclopentene (147 mg) in a mixture of tetrahydrofuran (5 ml) and water (2 ml) were added sodium azide (128 mg) and tetrakis(triphenylphosphine)-

palladium(0) (21.7 mg), and the mixture was stirred for 1.5 hours at 52°C. The resulting mixture was diluted with ethyl acetate and washed successively with water and brine. The organic layer was dried over sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a mixture of n-hexane and ethyl acetate (9:1) to give (1*R*,4*S*)-1-azido-4-(*tert*-butyldimethylsilyloxy)-2-cyclopentene (118 mg) as an oil.
NMR ($CDCl_3$, δ): 0.09 (6H, s), 0.90 (9H, s), 1.67 (1H, dt, J=5, 14Hz), 2.66 (1H, dt, J=7, 14Hz), 4.12 (1H, m), 4.74 (1H, m), 5.84 (1H, m), 5.99 (1H, m)

(2) (1*R*,3*S*)-1-Amino-3-(*tert*-butyldimethylsilyloxy)-cyclopentane (97 mg) was prepared from (1*R*,4*S*)-1-azido-4-(*tert*-butyldimethylsilyloxy)-2-cyclopentene (114 mg) in a similar manner to Example 29-(3).
NMR ($CDCl_3$, δ): 0.05 (6H, s), 0.88 (9H, s), 1.39-2.05 (6H, m), 3.28 (1H, m), 4.24 (1H, m)

(3) 2-[(1*R*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-cyclopentylamino]-5-cyano-*N*-(3,4-dimethoxybenzyl)benzamide (222 mg) was prepared from 5-cyano-2-fluoro-*N*-(3,4-dimethoxybenzyl)benzamide (122 mg) and (1*R*,3*S*)-1-amino-3-(*tert*-butyldimethylsilyloxy)cyclopentane (100 mg) in a similar manner to Example 12-(2).
This compound was used in the next step without purification.

(4) To a solution of 2-[(1*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)cyclopentylamino]-5-cyano-*N*-(3,4-dimethoxybenzyl)benzamide (200 mg) in tetrahydrofuran (1 ml) was added tetra-n-butylammonium fluoride (1M solution in tetrahydrofuran (3 ml), and the mixture was stirred at 20°C for 1 hour. The resulting mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was dried over sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a mixture of chloroform and ethyl acetate (2:1) to give 5-cyano-N-(3,4-dimethoxybenzyl)-2-[(1*R*,3*S*)-3-hydroxycyclopentylamino]benzamide (52 mg) as a solid.
NMR (DMSO-d_6, δ): 1.36 (1H, m), 1.50-1.77 (3H, m), 2.03 (1H, m), 2.24 (1H, m), 3.34 (2H, m), 3.72 (3H, s), 3.74 (3H, s), 3.87 (1H, m), 4.15 (1H, m), 4.34 (2H, d, J=6Hz), 4.67 (1H, d, J=4Hz), 6.77 (1H, d, J=9Hz), 6.83 (1H, dd, J=2, 8Hz), 6.88-6.96 (2H, m), 7.61 (1H, dd, J=2, 9Hz), 8.03 (1H,

d, J=2Hz), 8.78 (1H, d, J=7Hz), 8.97 (1H, t, J=6Hz)

Example 45

(1) 2-[(1*R*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-cyclopentylamino]-*N*-(3-chloro-4-methoxybenzyl)-5-cyanobenzamide (76 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-5-cyano-2-flurobenzamide (75 mg) and (1*R*,3*S*)-1-amino-3-(*tert*-butyldimethylsilyloxy)cyclopentane (61 mg) in a similar manner to Example 12-(2).

This compound was used in the next step without purification.

(2) 2-[(2*R*,3*S*)-3-Hydroxycyclopentylamino]-*N*-(3-chloro-4-methoxybenzyl)-5-cyanobenzamide (30 mg) was prepared from 2-[(1*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)cyclopentylamino]-*N*-(3-chloro-4-methoxybenzyl)-5-cyanobenzamide (73 mg) in a similar manner to Example 44-(4).

NMR (DMSO-d_6, δ): 1.36 (1H, m), 1.50-1.77 (3H, m), 2.03 (1H, m), 2.24 (1H, m), 3.83 (3H, s), 3.87 (1H, m), 4.15 (1H, m), 4.34 (2H, d, J=6Hz), 4.67 (1H, d, J=4Hz), 6.78 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.26 (1H, dd, J=2, 9Hz), 7.37 (1H, d, J=2Hz), 7.61 (1H, dd, J=2, 9Hz), 8.04 (1H, d, J=2Hz), 8.80 (1H, d, J=7Hz), 9.02 (1H, t, J=6Hz)

Example 46

(1) To a solution of *r*-1,*c*-3,*c*-5-cyclohexanetriol dihydrate (970 mg; water was removed by azeotropic distillation with ethanol-toluene) and carbontetrabromide (2.11 g) in dimethylformamide (4 ml) was added triphenylphosphine (1.51 g), and the mixture was stirred for 3 hours at ambient temperature. The resulting mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was dried over sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with 10% methanol in chloroform to give *t*-5-bromo-*r*-1,*c*-3-cyclohexanediol (224 mg) as a solid.

NMR (DMSO-d_6, δ): 1.18 (1H, m), 1.61 (2H, m), 2.02-2.15 (3H, m), 3.85 (2H, m), 4.78 (1H, m), 4.16-4.29 (2H, m)

(2) *c*-5-Azido-*r*-1,*c*-3-cyclohexanediol (26 mg) was prepared from *t*-5-bromo-*r*-1,*c*-3-cyclohexanediol (207 mg) and sodium azide (145 mg) in a similar manner to Example 34-(2).

NMR ($CDCl_3$, δ): 1.20-1.39 (3H, m), 2.18-2.30 (3H, m), 3.32 (1H, m), 3.65 (2H, m)

(3) *c*-5-Amino-*r*-1,*c*-3-cyclohexanediol(54 mg) was prepared from *c*-5-azido-*r*-1,*c*-3-cyclohexanediol (100 mg) in a similar manner to Example 29-(3).
NMR (DMSO-d_6, δ): 0.80 (2H, q, J=11Hz), 0.93 (2H, q, J=11Hz), 1.84 (2H, m), 1.96 (1H, m), 2.45 (1H, m), 4.48 (2H, m)

(4) 5-Cyano-2-(*c*-3,*c*-5-dihydroxy-*r*-1-cyclohexylamino)-*N*-(3,4-dimethoxybenzyl)benzamide (54 mg) was prepared from 5-cyano-2-fluoro-*N*-(3,4-dimethoxybenzyl)benzamide (108 mg) and *c*-5-amino-*r*-1,*c*-3-cyclohexanediol (54 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 0.93-1.20 (3H, m), 2.03-2.14 (3H, m), 3.43-3.62 (3H, m), 3.74 (3H, s), 3.76 (3H, s), 4.46 (1H, d, J=6Hz), 4.73 (1H, d, J=5Hz), 6.81-6.99 (4H, m), 7.63 (1H, dd, J=2, 9Hz), 8.08 (1H, d, J=2Hz), 8.61 (1H, d, J=8Hz), 9.08 (1H, t, J=6Hz)

Example 47

N-(3-Chloro-4-methoxybenzyl)-5-cyano-2-(*c*-3,*c*-5-dihydroxy-*r*-1-cyclohexylamino)benzamide (55 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-5-cyano-2-fluorobenzamide (98 mg) and *c*-5-amino-*r*-1,*c*-3-cyclohexanediol (48 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 0.93-1.20 (3H, m), 2.03-2.14 (3H, m), 3.43-3.62 (3H, m), 3.85 (3H, s), 4.36 (1H, d, J=6Hz), 4.71 (1H, d, J=5Hz), 6.84 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.27 (1H, dd, J=2, 9Hz), 7.37 (1H, d, J=2Hz), 7.64 (1H, dd, J=2, 9Hz), 8.09 (1H, d, J=2Hz), 8.61 (1H, d, J=7Hz), 9.07 (1H, t, J=5Hz)

Example 48

N-(3-Chloro-4-methoxybenzyl)-2-(*c*-3,*c*-5-dihydroxy-*r*-1-cyclohexylamino)-5-trifluoromethylbenzamide (38 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-2-fluoro-5-trifluoromethylbenzamide (101 mg) and *c*-5-amino-*r*-1,*c*-3-cyclohexanediol (44 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 0.92-1.18 (3H, m), 2.02-2.16 (3H, m), 3.38-3.64 (3H, m), 3.83 (3H, s), 4.36 (1H, d, J=6Hz), 4.68 (1H, d, J=6Hz), 6.88 (1H, d,

J=9Hz), 7.12 (1H, d, J=9Hz), 7.26 (1H, dd, J=2, 9Hz), 7.37 (1H, d, J=2Hz), 7.54 (1H, dd, J=2, 9Hz), 7.95 (1H, d, J=2Hz), 8.38 (1H, d, J=8Hz), 9.13 (1H, t, J=6Hz)

Example 49

N-(3-Chloro-4-methoxybenzyl)-5-cyano-2-(*c*-3,*c*-4-dihydroxy-*r*-1-cyclopentylamino)benzamide (83 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-5-cyano-2-fluorobenzamide (122 mg) and *c*-4-amino-*r*-1,*c*-2-cyclopentanediol (54 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 1.45 (2H, m), 2.25 (2H, m), 3.83 (3H, s), 3.66-3.90 (3H, m), 4.34 (2H, d, J=6Hz), 4.56 (1H, d, J=4Hz), 6.73 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.26 (1H, dd, J=2, 9Hz), 7.38 (1H, d, J=2Hz), 7.60 (1H, dd, J=2, 9Hz), 8.03 (1H, d, J=2Hz), 8.77 (1H, d, J=7Hz), 9.01 (1H, t, J=6Hz)

Example 50

(1) *t*-5-Bromo-*r*-1,*c*-3-dimethoxycyclohexane (105 mg) was prepared from *t*-5-bromo-*r*-1,*c*-3-cyclohexanediol (113 mg) in a similar manner to Example 38.
NMR ($CDCl_3$, δ): 1.26 (1H, m), 1.72 (2H, ddd, J=3, 7, 14Hz), 2.34-2.52 (3H, m), 3.38 (6H, s), 3.69 (2H, m), 4.68 (1H, q, J=4Hz)

(2) *c*-5-Azido-*r*-1,*c*-3-dimethoxycyclohexane (68 mg) was prepared from *t*-5-bromo-*r*-1,*c*-3-dimethoxycyclohexane (101 mg) in a similar manner to Example 34-(2).
NMR ($CDCl_3$, δ): 1.14 (1H, q, J=12Hz), 1.29 (2H, q, J=12Hz), 2.32-2.52 (3H, m), 3.12-3.30 (3H, m), 3.37 (6H, s)

(3) *c*-5-Amino-*r*-1,*c*-3-dimethoxycyclohexane (45 mg) was prepared from *c*-5-azido-*r*-1,*c*-3-dimethoxycyclohexane (65 mg) in a similar manner to Example 29-(3).
NMR ($CDCl_3$, δ): 1.03 (2H, q, J=12Hz), 1.09 (1H, q, J=12Hz), 2.15-2.26 (2H, m), 2.43 (1H, m), 2.68 (1H, m), 3.18 (2H, m), 3.37 (6H, s)

(4) 5-Cyano-2-(*c*-3,*c*-5-dimethoxy-*r*-1-cyclohexylamino)-*N*-(3,4-dimethoxybenzyl)benzamide (72 mg) was prepared from 5-cyano-2-fluoro-*N*-(3,4-dimethoxybenzyl)benzamide (74 mg) and *c*-5-amino-*r*-1,*c*-

3-dimethoxycyclohexane (45 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 0.94-1.12 (3H, m), 2.25 (2H, m), 2.39 (1H, m), 3.25 (6H, s), 3.20-3.34 (2H, m), 3.52 (1H, m), 3.72 (3H, s), 3.74 (3H, s), 4.35 (1H, d, J=6Hz), 6.81-7.05 (4H, m), 7.63 (1H, dd, J=2, 9Hz), 8.06 (1H, d, J=2Hz), 8.64 (1H, d, J=8Hz), 9.02 (2H, t, J=6Hz)

Example 51

N-(3-Chloro-4-methoxybenzyl)-5-cyano-2-(1,3-dioxan-5-ylamino)benzamide (25 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-5-cyano-2-fluorobenzamide (110 mg) and 5-amino-1,3-dioxane (43 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 3.72-3.82 (3H, m), 3.96-4.03 (2H, m), 4.36 (2H, d, J=6Hz), 4.79 (1H, d, J=6Hz), 4.87 (1H, d, J=6Hz), 6.89 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.28 (1H, dd, J=2, 9Hz), 7.39 (1H, d, J=2Hz), 7.63 (1H, dd, J=2, 9Hz), 8.10 (1H, d, J=2Hz), 9.08 (1H, t, J=6Hz), 9.13 (1H, d, J=7Hz)

Example 52

(1) Benzyl *N*-(*t*-3,*t*-4-dimethoxy-*r*-1-cyclopentyl)carbamate (80 mg) was prepared from benzyl *N*-(*t*-3,*t*-4-dihydroxy-*r*-1-cyclopentyl)carbamate (181 mg) in a similar manner to Example 38.
NMR ($CDCl_3$, δ): 1.55-1.71 (2H, m), 2.24-2.36 (2H, m), 3.37 (6H, s), 3.84 (2H, m), 4.22 (1H, m), 4.74 (1H, m), 5.09 (2H, s), 7.27-7.40 (5H, m)

(2) *t*-3,*t*-4-Dimethoxy-*r*-1-cyclopentylamine (40 mg) was prepared from benzyl *N*-(*t*-3,*t*-4-dimethoxy-*r*-1-cyclopentyl)carbamate (76 mg) in a similar manner to Example 29-(3).
NMR ($CDCl_3$, δ): 1.44-1.56 (2H, m), 2.11-2.23 (2H, m), 3.38 (6H, s), 3.64 (1H, m), 3.88 (2H, m)

(3) 5-Cyano-*N*-(3,4-dimethoxybenzyl)-2-(*t*-3,*t*-4-dimethoxy-*r*-1-cyclopentylamino)benzamide (43 mg) was prepared from 5-cyano-2-fluoro-*N*-(3,4-dimethoxybenzyl)benzamide (128 mg) and *t*-3,*t*-4-dimethoxy-*r*-1-cyclopentylamine (62 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 1.56 (2H, m), 2.24 (2H, m), 3.27 (6H, s), 3.72 (3H, s), 3.74 (3H, s), 3.83 (2H, m), 3.97 (1H, m), 4.35 (2H, d, J=6Hz), 6.73 (1H, d,

J=9Hz), 6.83 (1H, dd, J=2, 8Hz), 6.88-6.94 (2H, m), 7.61 (1H, dd, J=2, 9Hz), 8.06 (1H, d, J=2Hz), 8.69 (1H, d, J=7Hz), 9.03 (1H, t, J=6Hz)

Example 53

(1) To a solution of (1*R*,4*S*)-1-azido-4-(*tert*-butyldimethylsilyloxy)-2-cyclopentene (148 mg) in diethyl ether (3 ml) was added a 1M solution of lithium aluminum hydride in tetrahydrofuran (0.74 ml), and the mixture was stirred for 1 hour at 0°C. The resulting mixture was quenched with a diluted sodium hydroxide solution, filtered through a celite pad and washed with 10% aqueous solution of tetrahydrofuran. The filtrate and the washings were combined, dried over sodium sulfate, and evaporated *in vacuo* to give (1*R*,4*S*)-1-amino-4-(*tert*-butyldimethylsilyloxy)-2-cyclopentene (73 mg) as an oil.
NMR ($CDCl_3$, δ): 0.08 (6H, s), 0.90 (9H, s), 1.30 (1H, dt, J=13, 6Hz), 2.67 (1H, dt, J=13, 7Hz), 3.73 (1H, m), 4.70 (1H, m), 5.75 (1H, m), 5.83 (1H, m)

(2) *N*-(3-Chloro-4-methoxybenzyl)-5-cyano-2-[(1*R*,4*S*)-4-hydroxy-2-cyclopenten-1-ylamino]benzamide (77 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-5-cyano-2-fluorobenzamide (96 mg) and (1*R*,4*S*)-1-amino-4-(*tert*-butyldimethylsilyloxy)-2-cyclopentene (71 mg) in a similar manner to Examples 12-(2) and 44-(4).
NMR (DMSO-d_6, δ): 1.26 (1H, dt, J=13, 5Hz), 2.82 (3H, dq, J=13, 6Hz), 3.83 (3H, s), 3.87 (1H, m), 4.15 (1H, m), 4.34 (2H, d, J=6Hz), 4.47 (1H, m), 4.60 (1H, m), 5.07 (1H, d, J=6Hz), 5.87 (1H, m), 5.96 (1H, m), 6.93 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.26 (1H, dd, J=2, 9Hz), 7.37 (1H, d, J=2Hz), 7.64 (1H, dd, J=2, 9Hz), 8.07 (1H, d, J=2Hz), 8.74 (1H, d, J=8Hz), 9.07 (1H, t, J=6Hz)

Example 54

N-(3-Chloro-4-methoxybenzyl)-2-(*t*-3,*t*-4-dihydroxy-*r*-1-cyclopentylamino)-5-trifluoromethylbenzamide (149 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-2-fluoro-5-trifluoromethylbenzamide (188 mg) and *t*-4-amino-*r*-1,*c*-2-cyclopentanediol (73 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 1.55 (2H, m), 2.12 (2H, m), 3.83 (3H, s), 3.94-4.08 (3H, m), 4.35 (2H, d, J=6Hz), 4.53 (2H, d, J=4Hz), 6.74 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.27 (1H, dd, J=2, 9Hz), 7.37 (1H, d, J=2Hz), 7.56

(1H, dd, J=2, 9Hz), 7.95 (1H, d, J=2Hz), 8.46 (1H, d, J=6Hz), 9.13 (1H, t, J=6Hz)

Example 55

(1) To a solution of (1*S*,2*R*,4*R*)-1,2-cyclohexylidenedioxy-4-cyclohexanol (1.62 g) and carbon tetrabromide (2.91 g) in dichloromethane (12 ml) was added triphenylphosphine (2.2 g), and the mixture was stirred at ambient temperature for 1 hour. The solvent was evaporated *in vacuo* and the residue was diluted with ethyl acetate and washed successively with a sodium bicarbonate solution and brine. The organic layer was dried over sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with 10% ethyl acetate in n-hexane to give (1*S*,2*R*,4*S*)-4-bromo-1,2-cyclohexylidene-dioxycyclohexane (1.3 g).

NMR ($CDCl_3$, δ): 1.34-1.50 (2H, m), 1.50-1.75 (8H, m), 1.72-1.94 (2H, m), 2.03-2.40 (4H, m), 4.14 (1H, m), 4.28 (1H, m), 4.43 (1H, m)

(2) (1*S*,2*R*,4*R*)-4-Azido-1,2-cyclohexylidenedioxycyclohexane (126 mg) was prepared from (1*S*,2*R*,4*S*)-4-bromo-1,2-cyclohexylidenedioxycyclo-hexane (148 mg) and sodium azide (74 mg) in a similar manner to Example 34-(2).

NMR ($CDCl_3$, δ): 1.34-1.50 (2H, m), 1.50-1.85 (12H, m), 2.09-2.29 (2H, m), 3.25 (1H, m), 4.08-4.19 (2H, m)

(3) (1*S*,2*R*,4*R*)-4-Amino-1,2-cyclohexylidenedioxycyclohexane (107 mg) was prepared from (1*S*,2*R*,4*R*)-4-azido-1,2-cyclohexylidenedioxycyclo-hexane (121 mg) in a similar manner to Example 29-(3).

NMR ($CDCl_3$, δ): 1.33-1.78 (14H, m), 1.95-2.18 (2H, m), 2.74 (1H, m), 4.10-4.20 (2H, m)

(4) *N*-(3-Chloro-4-methoxybenzyl)-5-cyano-2-[(1*R*,3*R*,4*S*)-3,4-cyclohexylidenedioxycyclohexylamino]benzamide (134 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-5-cyano-2-fluorobenzamide (140 mg) and (1*S*,2*R*,4*R*)-4-amino-1,2-cyclohexylidenedioxycyclohexane (102 mg) in a similar manner to Example 12-(2).

NMR (DMSO-d_6, δ): 1.24-1.90 (15H, m), 2.04 (1H, m), 3.58 (1H, m), 3.83

(3H, s), 4.09 (1H, m), 4.19 (1H, m), 4.34 (2H, d, J=6Hz), 6.84 (1H, d, J=9Hz), 7.10 (1H, d, J=9Hz), 7.24 (1H, dd, J=2, 9Hz), 7.35 (1H, d, J=2Hz), 7.59 (1H, dd, J=2, 9Hz), 8.03 (1H, d, J=2Hz), 8.70 (1H, d, J=7Hz), 9.01 (1H, t, J=6Hz)

(5) To a solution of *N*-(3-chloro-4-methoxybenzyl)-5-cyano-2-[(1*R*,3*R*,4*S*)-3,4-cyclohexylidenedioxycyclohexylamino]benzamide (130 mg) in dioxane (2 ml) was added 1*N*-hydrochloric acid (0.5 ml), and the mixture was stirred at 20°C for 2 hours. The resulting mixture was diluted with ethyl acetate and washed successively with a sodium bicarbonate solution and brine. The organic layer was dried over sodium sulfate and evaporated *in vacuo*. The residue was recrystallized from a mixture of ethyl acetate and diethyl ether to give *N*-(3-chloro-4-methoxybenzyl)-5-cyano-2-[(1*R*,3*R*,4*S*)-3,4-dihydroxycyclohexylamino]-benzamide (66 mg).
NMR (DMSO-d_6, δ): 1.38-1.84 (6H, m), 3.43-3.59 (2H, m), 3.68 (1H, m), 3.83 (3H, s), 4.28-4.38 (3H, m), 4.53 (1H, d, J=5Hz), 6.86 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.27 (1H, dd, J=2, 9Hz), 7.37 (1H, d, J=2Hz), 7.60 (1H, dd, J=2, 9Hz), 8.03 (1H, d, J=2Hz), 8.67 (1H, d, J=7Hz), 9.02 (1H, t, J=5Hz)

Example 56

(1) (1*S*,2*R*,4*R*)-4-(4-Toluenesulfonyloxy)-1,2-cyclohexylidenedioxycyclohexane (164 mg) was prepared from (1*S*,2*R*,4*R*)-1,2-cyclohexylidenedioxy-4-cyclohexanol (172 mg) and *p*-toluenesulfonyl chloride (170 mg) in a similar manner to Example 34-(1).
NMR ($CDCl_3$, δ): 1.33-1.43 (2H, m), 1.50-1.88 (12H, m), 2.02-2.20 (2H, m), 2.45 (3H, s), 4.01-4.09 (2H, m), 4.39 (1H, m), 7.33 (2H, d, J=8Hz), 7.79 (2H, d, J=8Hz)

(2) (1*S*,2*R*,4*S*)-4-Azido-1,2-cyclohexylidenedioxycyclohexane (100 mg) was prepared from (1*S*,2*R*,4*R*)-4-(4-toluenesulfonyloxy)-1,2-cyclohexylidenedioxycyclohexane (160 mg) and sodium azide (60 mg) in a similar manner to Example 34-(2).
NMR ($CDCl_3$, δ): 1.34-1.48 (3H, m), 1.50-1.82 (10H, m), 1.86-2.01 (2H, m), 2.18 (1H, m), 3.76 (1H, m), 4.11 (1H, m), 4.27 (1H, q, J=5Hz)

(3) (1*S*,2*R*,4*S*)-4-Amino-1,2-cyclohexylidenedioxycyclohexane (90 mg) was prepared from (1*S*,2*R*,4*S*)-4-azido-1,2-cyclohexylidenedioxyyclohexane (97 mg) in a similar manner to Example 29-(3).
NMR ($CDCl_3$, δ): 1.08 (1H, m), 1.31-1.96 (13H, m), 2.12-2.29 (4H, m), 3.07 (1H, m), 4.05 (1H, m), 4.27 (1H, m)

(4) *N*-(3-Chloro-4-methoxybenzyl)-5-cyano-2-[(1*S*,3*R*,4*S*)-3,4-cyclohexylidenedioxycyclohexylamino]benzamide (140 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-5-cyano-2-fluorobenzamide (120 mg) and (1*S*,2*R*,4*S*)-4-amino-1,2-cyclohexylidenedioxycyclohexane (87 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 1.22 (1H, m), 1.29-1.40 (2H, m), 1.44-1.92 (12H, m), 2.17 (1H, m), 3.67 (1H, m), 3.83 (3H, s), 4.09 (1H, m), 4.24 (1H, m), 4.34 (2H, d, J=6Hz), 6.84 (1H, d, J=9Hz), 7.10 (1H, d, J=9Hz), 7.25 (1H, dd, J=2, 9Hz), 7.36 (1H, d, J=2Hz), 7.63 (1H, dd, J=2, 9Hz), 8.06 (1H, d, J=2Hz), 8.65 (1H, d, J=7Hz), 9.07 (1H, t, J=6Hz)

(5) *N*-(3-Chloro-4-methoxybenzyl)-5-cyano-2-[(1*S*,3*R*,4*S*)-3,4-dihydroxycyclohexylamino]benzamide (69 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-5-cyano-2-[(1*S*,3*R*,4*S*)-3,4-cyclohexylidenedioxycyclohexylamino]benzamide (135 mg) in a similar manner to Example 55-(5).
NMR (DMSO-d_6, δ): 1.26 (1H, m), 1.41 (1H, m), 1.53 (1H, m), 1.71 (1H, m), 1.82-2.02 (2H, m), 3.52 (1H, m), 3.66-3.80 (2H, m), 3.83 (3H, s), 4.34 (2H, d, J=6Hz), 4.44 (1H, d, J=5Hz), 4.50 (1H, d, J=4Hz), 6.79 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.25 (1H, dd, J=2, 9Hz), 7.37 (1H, d, J=2Hz), 7.63 (1H, dd, J=2, 9Hz), 8.06 (1H, d, J=2Hz), 8.64 (1H, d, J=8Hz), 9.03 (1H, t, J=5Hz)

Example 57

(1) To a suspension of 2-fluoro-5-nitrobenzoic acid (10.0 g) in dry dichloromethane (100 ml) was added oxalyl chloride (5.18 ml), followed by dimethylformamide (0.5 ml). After stirring for 1 hour at 20°C, the reaction mixture was evaporated *in vacuo*. The residue was redissolved in dichloromethane (100 ml) and then triethylamine (7.53 ml) was added, followed by 3,4-dimethoxybenzylamine (9.30 g). After stirring for 3 hours at 20°C, the reaction mixture was washed with water, a saturated

sodium bicarbonate solution, water, 1*N*-hydrochloric acid, water and brine, successively, and dried over magnesium sulfate. After evaporation of the solvent, the residue was triturated with methanol to give *N*-(3,4-dimethoxybenzyl)-2-fluoro-5-nitrobenzamide (14.2 g) as pale yellow crystals.
NMR ($CDCl_3$, δ): 3.89 (6H, s), 4.63 (2H, d, J=7Hz), 6.84-6.93 (4H, m), 7.30 (1H, m), 8.35 (1H, m), 9.03 (1H, m)

(2) *N*-(3,4-Dimethoxybenzyl)-2-((*S*)-2-hydroxy-1-methylethylamino)-5-nitrobenzamide (188 mg) was prepared from *N*-(3,4-dimethoxybenzyl)-2-fluoro-5-nitrobenzamide (200 mg) and (*S*)-2-amino-1-propanol (90 mg) in a similar manner to Example 12-(2) as a yellow powder.
mp: 131-132°C
NMR (DMSO-d_6, δ): 1.16 (3H, d, J=6Hz), 3.46 (2H, m), 3.68-3.81 (1H, m), 3.73 (3H, s), 3.74 (3H, s), 4.37 (2H, d, J=6Hz), 4.99 (1H, t, J=5Hz), 6.82-6.98 (4H, m), 8.11 (1H, dd, J=9, 3Hz), 8.58 (1H, d, J=3Hz), 9.10 (1H, d, J=8Hz), 9.29 (1H, t, J=6Hz)

Example 58

(1) *N*-(3-Chloro-4-methylbenzyl)-2-fluoro-5-nitrobenzamide (2.25 g) was prepared from 2-fluoro-5-nitrobenzoic acid (1.65 g) and 3-chloro-4-methylbenzylamine (1.46 g) in a similar manner to Example 66-(1) as a pale yellow powder.
NMR (DMSO-d_6, δ): 2.31 (3H, s), 4.46 (2H, d, J=6Hz), 7.23 (1H, dd, J=8, 1Hz), 7.33 (1H, d, J=8Hz), 7.39 (1H, d, J=1Hz), 7.64 (1H, dd, J=9, 9Hz), 8.37-8.50 (2H, m), 9.19 (1H, t, J=6Hz)

(2) *N*-(3-Chloro-4-methylbenzyl)-2-(*trans*-4-hydroxycyclohexylamino)-5-nitrobenzamide (446 mg) was prepared from *N*-(3-chloro-4-methylbenzyl)-2-fluoro-5-nitrobenzamide (426 mg) and *trans*-aminocyclohexanol (304 mg) in a similar manner to Example 12-(2) as a yellow powder.
mp: 213-215°C
NMR ($CDCl_3$, δ): 1.19-1.43 (4H, m), 1.72-1.87 (2H, m), 1.90-2.05 (2H, m), 2.30 (3H, s), 3.40-3.58 (2H, m), 4.39 (2H, d, J=6Hz), 4.61 (1H, d, J=5Hz), 6.91 (1H, d, J=10Hz), 7.19 (1H, dd, J=8, 1Hz), 7.32 (1H, d, J=8Hz), 7.35 (1H, d, J=1Hz), 8.12 (1H, dd, J=10, 2Hz), 8.62 (1H, d, J=2Hz), 9.07 (1H, d,

J=8Hz), 9.39 (1H, t, J=6Hz)

(3) To a mixture of *N*-(3-chloro-4-methylbenzyl)-2-(*trans*-4-hydroxy-cyclohexylamino)-5-nitrobenzamide (309 mg), benzoic acid (108 mg) and diethyl azodicarboxylate (155 mg) in anhydrous tetrahydrofuran (10 ml) was added triphenylphosphine (233 mg). After stirring for 15 hours at ambient temperature, the mixture was evaporated *in vacuo*. The residue was purified by a silica gel column chromatography eluting with a mixture of n-hexane and ethyl acetate (4:1) to give 2-(*cis*-4-benzoyloxy-cyclohexylamino)-*N*-(3-chloro-4-methylbenzyl)-5-nitrobenzamide (132 mg) as a yellow powder.
NMR ($CDCl_3$, δ): 1.59-1.79 (2H, m), 1.80-1.98 (6H, m), 2.29 (3H, s), 3.75 (1H, m), 4.43 (2H, d, J=6Hz), 5.14 (1H, m), 6.98 (1H, d, J=10Hz), 7.20 (1H, dd, J=8, 1Hz), 7.31 (1H, d, J=8Hz), 7.37 (1H, d, J=1Hz), 7.46-7.71 (3H, m), 8.01 (2H, d, J=8Hz), 8.15 (1H, dd, J=10, 3Hz), 8.65 (1H, d, J=3Hz), 9.25 (1H, d, J=8Hz), 9.43 (1H, t, J=6Hz)

(4) A mixture of 2-(*cis*-4-benzoyloxycyclohexylamino)-*N*-(3-chloro-4-methylbenzyl)-5-nitrobenzamide (120 mg), methanol (3 ml), tetrahydrofuran (3 ml) and 1*N* sodium hydroxide solution (0.5 ml) was stirred for 3 hours at 60°C. After evaporation of the organic solvent, the aqueous layer was diluted with water and extracted with diethyl ether. The extract was washed with brine, dried over magnesium sulfate, and evaporated *in vacuo*. The residue was purified by a silica gel column chromatography eluting with a mixture of n-hexane and ethyl acetate (2:1). The crude product was triturated with a mixture of n-hexane and ethyl acetate (1:1) to give *N*-(3-chloro-4-methylbenzyl)-2-(*cis*-4-hydroxy-cyclohexyl)amino-5-nitrobenzamide as a yellow powder (64 mg).
mp: 189-190°C
NMR ($CDCl_3$, δ): 1.42-1.77 (8H, m), 2.31 (3H, s), 3.58-3.73 (2H, m), 4.42 (2H, d, J=5Hz), 4.54 (1H, d, J=4Hz), 6.89 (1H, d, J=10Hz), 7.20 (1H, d, J=8Hz), 7.32 (1H, d, J=8Hz), 7.37 (1H, s), 8.11 (1H, dd, J=10, 2Hz), 8.64 (1H, d, J=2Hz), 9.27 (1H, d, J=8Hz), 9.40 (1H, t, J=5Hz)

Example 59

A mixture of 5-cyano-*N*-(3-cyano-4-methoxybenzyl)-2-fluoro-benzamide (100 mg), *cis*-4-amino-1-methylcyclohexanol (83.5 mg) and

potassium carbonate (89.4 mg) in pyridine (2 ml) was heated for 2 hours at 80°C. The mixture was partitioned between ethyl acetate and 0.5*N*-hydrochloric acid. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated *in vacuo*. The residue was purified by a preparative thin layer chromatography on silica gel eluting with 10% methanol in chloroform to give 5-cyano-*N*-(3-cyano-4-methoxybenzyl)-2-(*c*-4-hydroxy-*t*-4-methyl-*r*-1-cyclohexylamino)-benzamide (87 mg) as colorless crystals.

mp: 207-208°C

NMR (DMSO-d_6, δ): 1.12 (3H, s), 1.40-1.65 (6H, m), 1.67-1.77 (2H, m), 3.60 (1H, m), 3.90 (3H, s), 4.37 (2H, d, J=5Hz), 6.84 (1H, d, J=9Hz), 7.23 (1H, d, J=9Hz), 7.56-7.66 (2H, m), 8.06 (1H, d, J=2Hz), 8.62 (1H, d, J=9Hz), 9.09 (1H, t, J=5Hz)

Example 60

5-Cyano-*N*-(3-cyano-4-methoxybenzyl)-2-(*t*-4-hydroxy-*c*-4-methyl-*r*-1-cyclohexylamino)benzamide (92 mg) was prepared from 5-cyano-*N*-(3-cyano-4-methoxybenzyl)-2-fluorobenzamide (100 mg) and *trans*-4-amino-1-methylcyclohexanol (83.5 mg) in a similar manner to Example 59 as colorless crystals.

mp: 216-217°C

NMR (DMSO-d_6, δ): 1.11 (3H, s), 1.33-1.46 (6H, m), 1.85-1.97 (2H, m), 3.50 (1H, m), 3.90 (3H, s), 4.37 (2H, d, J=5Hz), 6.83 (1H, d, J=9Hz), 7.22 (1H, d, J=9Hz), 7.58-7.65 (2H, m), 8.07 (1H, d, J=2Hz), 8.39 (1H, d, J=9Hz), 9.07 (1H, t, J=5Hz)

Example 61

(1) Methyl 5-cyano-2-(*trans*-4-hydroxycyclohexylamino)-benzoate (1.77 g) was prepared from methyl 5-cyano-2-fluorobenzoate (1.3 g) and *trans*-4-aminocyclohexanol (1.25 g) in a similar manner to Example 12-(2) as a yellow powder.

NMR ($CDCl_3$, δ): 1.32-1.55 (4H, m), 1.96-2.21 (4H, m), 3.35-3.51 (1H, m), 3.69-3.81 (1H, m), 3.97 (3H, s), 6.70 (1H, d, J=8Hz), 7.50 (1H, dd, J=8, 2Hz), 8.21 (1H, d, J=2Hz), 8.31 (1H, d, J=8Hz)

(2) To a solution of methyl 5-cyano-2-(*trans*-4-hydroxycyclohexyl-amino)benzoate (1.5 g) in tetrahydrofuran (30 ml) were added acetic acid

(394 mg) and diethyl azodicarboxylate (1.05 g) at 0°C, followed by triphenylphosphine (1.58 g). After stirring for 1.5 hours at ambient temperature, the mixture was evaporated *in vacuo*. The residue was purified by a silica gel column chromatography eluting with a mixture of n-hexane and ethyl acetate (4:1) to give methyl 2-(*cis*-4-acetoxycyclohexylamino)-5-cyanobenzoate (1.0 g) as a yellow powder.
NMR ($CDCl_3$, δ): 1.65-1.96 (8H, m), 2.08 (3H, s), 3.55 (1H, br), 3.90 (3H, s), 4.95 (1H, br), 6.70 (1H, d, J=8Hz), 7.50 (1H, dd, J=8, 2Hz), 8.23 (1H, d, J=2Hz), 8.48 (1H, br d, J=8Hz)

(3) 5-Cyano-2-(*cis*-4-hydroxycyclohexylamino)benzoic acid (695 mg) was prepared from methyl 5-cyano-2-(cis-4-acetoxycyclohexylamino)-benzoate (900 mg) in a similar manner to Example 58-(4) as a yellow powder.
NMR (DMSO-d_6, δ): 1.44-1.72 (8H, m), 3.65 (1H, br), 4.57 (1H, br), 6.91 (1H, d, J=8Hz), 7.16 (1H, dd, J=8, 2Hz), 8.10 (1H, d, J=2Hz), 8.64 (1H, br d, J=8Hz)

(4) 5-Cyano-*N*-(3,4-dimethoxybenzyl)-2-(*cis*-4-hydroxycyclohexylamino)benzamide (123 mg) was prepared from 5-cyano-2-(*cis*-4-hydroxycyclohexylamino)benzoic acid (80.0 mg) and 3,4-dimethoxybenzylamine (61.7 mg) in a similar manner to Example 1-(3) as a colorless powder.
NMR (DMSO-d_6, δ): 1.44-1.70 (8H, br), 3.53-3.71 (2H, br), 3.73 (3H, s), 3.74 (3H, s), 4.36 (2H, d, J=7Hz), 4.53 (1H, d, J=4Hz), 6.79-6.97 (4H, m), 7.60 (1H, dd, J=2, 8Hz), 8.06 (1H, d, J=2Hz), 8.84 (1H, d, J=8Hz), 9.01 (1H, br)

Example 62

N-(3-Chloro-4-methoxybenzyl)-5-cyano-2-[(*R*)-1-(hydroxymethyl)-propylamino]benzamide (158 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-5-cyano-2-fluorobenzamide (150 mg) and (*R*)-2-amino-1-butanol (83.9 mg) in a similar manner to Example 12-(2) as a colorless powder.
NMR (DMSO-d_6, δ): 0.89 (3H, t, J=7Hz), 1.35-1.54 (1H, br), 1.57-1.76 (1H, br), 3.38-3.54 (3H, br), 3.83 (3H, s), 4.34 (2H, d, J=7Hz), 4.85 (1H, d, J=7Hz), 6.85 (1H, d, J=8Hz), 7.11 (1H, d, J=8Hz), 7.26 (1H, dd, J=2, 8Hz),

7.37 (1H, d, J=2Hz), 7.58 (1H, dd, J=2, 8Hz), 8.04 (1H, d, J=2Hz), 8.72 (1H, d, J=8Hz), 9.03 (1H, br)

Example 63

N-(3-Chloro-4-methoxybenzyl)-5-cyano-2-[(*S*)-1-(hydroxymethyl)-propylamino]benzamide (150 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-5-cyano-2-fluorobenzamide (150 mg) and (*S*)-2-amino-1-butanol (83.9 mg) in a similar manner to Example 12-(2) as a colorless powder.

NMR (DMSO-d_6, δ): 0.89 (3H, t, J=7Hz), 1.35-1.54 (1H, br), 1.57-1.76 (1H, br), 3.38-3.54 (3H, br), 3.83 (3H, s), 4.34 (2H, d, J=7Hz), 4.85 (1H, d, J=7Hz), 6.85 (1H, d, J=8Hz), 7.11 (1H, d, J=8Hz), 7.26 (1H, dd, J=2, 8Hz), 7.37 (1H, d, J=2Hz), 7.58 (1H, dd, J=2, 8Hz), 8.04 (1H, d, J=2Hz), 8.72 (1H, d, J=8Hz), 9.03 (1H, br)

Example 64

N-(3-Chloro-4-methoxybenzyl)-5-cyano-2-(1,1-dimethyl-2-hydroxyethyl)aminobenzamide (61.6 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-5-cyano-2-fluorobenzamide (150 mg) and 2-amino-2-methyl-1-propanol (126 mg) in a similar manner to Example 12-(2) as a colorless powder.

NMR (DMSO-d_6, δ): 1.29 (6H, s), 3.40 (2H, d, J=7Hz), 3.83 (3H, s), 4.33 (2H, d, J=7Hz), 5.10 (1H, t, J=7Hz), 7.00 (1H, d, J=8Hz), 7.11 (1H, d, J=8Hz), 7.27 (1H, dd, J=2, 8Hz), 7.37 (1H, d, J=2Hz), 7.55 (1H, dd, J=2, 8Hz), 7.99 (1H, d, J=2Hz), 8.89 (1H, s), 9.00 (1H, br)

Example 65

N-(3-Chloro-4-methoxybenzyl)-5-cyano-2-(*cis*-4-hydroxycyclohexylamino)benzamide (105 mg) was prepared from 5-cyano-2-(*cis*-4-hydroxycyclohexylamino)benzoic acid (80.0 mg) and 3-chloro-4-methoxybenzylamine (63.3 mg) in a similar manner to Example 1-(3) as a colorless powder.

NMR (DMSO-d_6, δ): 1.45-1.70 (8H, br), 3.53-3.71 (2H, br), 3.83 (3H, s), 4.36 (2H, d, J=7Hz), 4.52 (1H, d, J=4Hz), 6.84 (1H, d, J=8Hz), 7.12 (1H, d, J=8Hz), 7.27 (1H, dd, J=2, 8Hz), 7.38 (1H, d, J=2Hz), 7.60 (1H, dd, J=2, 8Hz), 8.07 (1H, d, J=2Hz), 8.86 (1H, d, J=8Hz), 9.07 (1H, br)

Example 66

(1) To a mixture of 5-cyano-2-fluorobenzoic acid (1.00 g) and oxalyl chloride (0.74 ml) in dichloromethane (10 ml) was added dimethylformamide (10 drops), and the mixture was stirred for 1 hour at ambient temperature. After evaporation of the solvent, dichloromethane (20 ml), triethylamine (1.69 ml) and 4-chloro-3-methoxybenzylamine (1.07 g) were added to the residue under ice-water cooling, and the mixture was stirred for 2 hours at ambient temperature. The mixture was washed with water, 1*N*-hydrochloric acid, water, a saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated *in vacuo*. The residue was triturated with methanol to give *N*-(4-chloro-3-methoxybenzyl)-5-cyano-2-fluoro-benzamide as a colorless powder (1.24 g).

NMR (DMSO-d_6, δ): 3.85 (3H, s), 4.46 (2H, d, J=7Hz), 6.93 (1H, dd, J=2, 8Hz), 7.13 (1H, d, J=2Hz), 7.39 (1H, d, J=8Hz), 7.58 (1H, m), 8.06 (1H, m), 8.13 (1H, dd, J=2, 8Hz), 9.12 (1H, br)

(2) *N*-(4-Chloro-3-methoxybenzyl)-5-cyano-2-[(*S*)-1-(hydroxymethyl)-ethylamino]benzamide (95.0 mg) was prepared from *N*-(4-chloro-3-methoxybenzyl)-5-cyano-2-fluorobenzamide (100 mg) and (*S*)-2-amino-1-propanol (47.1 mg) in a similar manner to Example 12-(2) as a colorless powder.

NMR (DMSO-d_6, δ): 1.12 (3H, d, J=7Hz), 3.42 (2H, t, J=7Hz), 3.58-3.73 (1H, br), 3.85 (3H, s), 4.41 (2H, d, J=7Hz), 4.92 (1H, t, J=7Hz), 6.85 (1H, d, J=8Hz), 6.92 (1H, dd, J=2, 8Hz), 7.12 (1H, d, J=2Hz), 7.37 (1H, d, J=8Hz), 7.61 (1H, dd, J=2, 8Hz), 8.06 (1H, d, J=2Hz), 8.68 (1H, d, J=8Hz), 9.07 (1H, br)

Example 67

N-(4-Chloro-3-methoxybenzyl)-5-cyano-2-[(*S*)-1-(hydroxymethyl)-propylamino]benzamide (98.2 mg) was prepared from *N*-(4-chloro-3-methoxybenzyl)-5-cyano-2-fluorobenzamide (100 mg) and (*S*)-2-amino-1-butanol (55.9 mg) in a similar manner to Example 12-(2) as a colorless powder.

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=7Hz), 1.38-1.53 (1H, br), 1.58-1.75 (1H, br), 3.38-3.53 (3H, br), 3.85 (3H, s), 4.41 (2H, d, J=7Hz), 4.85 (1H, t, J=7Hz), 6.85 (1H, d, J=8Hz), 6.90 (1H, dd, J=2, 8Hz), 7.11 (1H, d, J=2Hz),

7.37 (1H, d, J=8Hz), 7.60 (1H, dd, J=2, 8Hz), 8.06 (1H, d, J=2Hz), 8.68 (1H, d, J=8Hz), 9.07 (1H, br)

Example 68

N-(4-Chloro-3-methoxybenzyl)-5-cyano-2-(1,1-dimethyl-2-hydroxyethylamino)benzamide (71.9 mg) was prepared from *N*-(4-chloro-3-methoxybenzyl)-5-cyano-2-fluorobenzamide (150 mg) and 2-amino-2-methyl-1-propanol (126 mg) in a similar manner to Example 12-(2) as a colorless powder.

NMR (DMSO-d_6, δ): 1.28 (6H, s), 3.39 (2H, d, J=7Hz), 3.85 (3H, s), 4.41 (2H, d, J=7Hz), 5.11 (1H, br), 6.91 (1H, dd, J=2, 8Hz), 7.00 (1H, d, J=8Hz), 7.11 (1H, d, J=2Hz), 7.37 (1H, d, J=8Hz), 7.55 (1H, dd, J=2, 8Hz), 8.01 (1H, d, J=2Hz), 8.85 (1H, s), 9.04 (1H, br)

Example 69

N-(4-Chloro-3-methoxybenzyl)-5-cyano-2-(*cis*-4-hydroxycyclohexylamino)benzamide (105 mg) was prepared from 5-cyano-2-(*cis*-4-hydroxycyclohexylamino)benzoic acid (80.0 mg) and 4-chloro-3-methoxybenzylamino (63.3 mg) in a similar manner to Example 1-(3) as a colorless powder.

NMR (DMSO-d_6, δ): 1.42-1.71 (8H, br), 3.53-3.70 (2H, br), 3.85 (3H, s), 4.43 (2H, d, J=7Hz), 4.52 (1H, d, J=4Hz), 6.84 (1H, d, J=8Hz), 6.91 (1H, d, J=8Hz), 7.13 (1H, s), 7.37 (1H, d, J=8Hz), 7.61 (1H, dd, J=2, 8Hz), 8.09 (1H, d, J=2Hz), 8.83 (1H, d, J=8Hz), 9.13 (1H, br)

Example 70

(1) 2-(*trans*-4-Aminocyclohexylamino)-*N*-(4-chloro-3-methoxybenzyl)-5-cyanobenzamide (220 mg) was prepared from *N*-(4-chloro-3-methoxybenzyl)-5-cyano-2-fluorobenzamide (200 mg) and *trans*-1,4-diaminocyclohexane (215 mg) in a similar manner to Example 12-(2) as a colorless powder.

NMR (DMSO-d_6, δ): 1.10-1.30 (4H, br), 1.68-1.85 (2H, br), 1.90-2.04 (2H, br), 2.55-2.65 (1H, br), 3.35-3.45 (1H, br), 3.85 (3H, s), 4.40 (2H, d, J=7Hz), 6.84 (1H, d, J=8Hz), 6.90 (1H, dd, J=2, 8Hz), 7.11 (1H, s), 7.37 (1H, d, J=8Hz), 7.60 (1H, dd, J=2, 8Hz), 8.07 (1H, d, J=2Hz), 8.58 (1H, d, J=8Hz), 9.09 (1H, br)

(2) To a mixture of 2-(*trans*-4-aminocyclohexylamino)-*N*-(4-chloro-3-methoxybenzyl)-5-cyanobenzamide (120 mg) in dimethylformamide (2 ml) was added ethyl formate (7 ml), and the mixture was heated under reflux for 5 hours. The mixture was partitioned between ethyl acetate and water. The separated organic layer was washed with water and brine, dried over magnesium sulfate, and evaporated *in vacuo*. The residue was purified by a silica gel column chromatography eluting with a mixture of chloroform and methanol (20:1). The crude product was triturated with diisopropyl ether to give N-(4-chloro-3-methoxybenzyl)-5-cyano-2-(*trans*-4-formamidocycylohexylamino)benzamide as a colorless powder (117 mg).

NMR (DMSO-d_6, δ): 1.17-1.46 (4H, br), 1.78-1.90 (2H, br), 1.93-2.04 (2H, br), 3.37-3.52 (1H, br), 3.57-3.73 (1H, br), 3.85 (3H, s), 4.41 (2H, d, J=7Hz), 6.92 (2H, m), 7.11 (1H, s), 7.37 (1H, d, J=8Hz), 7.61 (1H, dd, J=2, 8Hz), 7.94 (1H, s), 8.03 (1H, br),8.08 (1H, d, J=2Hz), 8.61 (1H, d, J=8Hz), 9.12 (1H, br)

Example 71

(1) To a solution of 3-cyano-4-methoxybenzyl bromide (15.0 g) in dimethylformamide (75 ml) was added potassium phthalimide (13.5 g), and the mixture was stirred for 1 hour at ambient temperature, and poured into water. The resulting precipitates were collected by filtration and washed with water, ethanol and then diisopropyl ether to give *N*-(3-cyano-4-methoxybenzyl)phthalimide as a colorless powder (15.8 g).

NMR ($CDCl_3$, δ): 3.89 (3H, s), 4.78 (2H, s), 6.92 (1H, d, J=8Hz), 7.62 (2H, m), 7.71 (2H, m), 7.84 (2H, m)

(2) To a solution of *N*-(3-cyano-4-methoxybenzyl)phthalimide (10.0 g) in ethanol (150 ml) was added hydrazine hydrate (8.30 ml), and the mixture was heated under reflux for 2 hours. The resulting precipitates were filtered off and the filtrates were evaporated *in vacuo*. The residue was partitioned between chloroform and a saturated sodium bicarbonate solution. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated *in vacuo* to give 3-cyano-4-methoxybenzylamine as a colorless powder (4.60 g).

NMR ($CDCl_3$, δ): 3.83 (2H, s), 3.91 (3H, s), 6.91 (1H, d, J=8Hz), 7.46-7.54

(2H, m)

(3) 5-Cyano-*N*-(3-cyano-4-methoxybenzyl)-2-fluorobenzamide (2.80 g) was prepared from 5-cyano-2-fluorobenzoic acid (1.50 g) and 3-cyano-4-methoxybenzylamine (1.62 g) in a similar manner to Example 1-(3) as a colorless powder.
NMR (DMSO-d_6, δ): 3.91 (3H, s), 4.42 (2H, d, J=7Hz), 7.23 (1H, d, J=8Hz), 7.52-7.67 (3H, m), 8.04 (1H, m), 8.15 (1H, dd, J=2, 8Hz), 9.08 (1H, br)

(4) 5-Cyano-*N*-(3-cyano-4-methoxybenzyl)-2-[(*R*)-1-(hydroxymethyl)ethylamino]benzamide (131 mg) was prepared from 5-cyano-*N*-(3-cyano-4-methoxybenzyl)-2-fluorobenzamide (120 mg) and (*R*)-2-amino-1-propanol (58.3 mg) in a similar manner to Example 12-(2) as a pale yellow powder.
NMR (DMSO-d_6, δ): 1.12 (3H, d, J=7Hz), 3.42 (2H, t, J=7Hz), 3.60-3.72 (1H, br), 3.90 (3H, s), 4.36 (2H, d, J=7Hz), 4.91 (1H, t, J=7Hz), 6.85 (1H, d, J=8Hz), 7.23 (1H, d, J=8Hz), 7.58-7.69 (3H, m), 8.06 (1H, d, J=2Hz), 8.71 (1H, d, J=8Hz), 9.04 (1H, br)

Example 72

5-Cyano-*N*-(3-cyano-4-methoxybenzyl)-2-[(*S*)-1-(hydroxymethyl)ethyl-amino]benzamide (124 mg) was prepared from 5-cyano-*N*-(3-cyano-4-methoxybenzyl)-2-fluorobenzamide (120 mg) and (*S*)-2-amino-1-propanol (58.3 mg) in a similar manner to Example 12-(2) as a colorless powder.
NMR (DMSO-d_6, δ): 1.12 (3H, d, J=7Hz), 3.42 (2H, t, J=7Hz), 3.60-3.73 (1H, br), 3.90 (3H, s), 4.36 (2H, d, J=7Hz), 4.92 (1H, t, J=7Hz), 6.85 (1H, d, J=8Hz), 7.23 (1H, d, J=8Hz), 7.58-7.71 (3H, m), 8.06 (1H, d, J=2Hz), 8.68 (1H, d, J=8Hz), 9.05 (1H, br)

Example 73

5-Cyano-*N*-(3-cyano-4-methoxybenzyl)-2-[(*R*)-1-(hydroxymethyl)-propylamino]benzamide (35.0 mg) was prepared from 5-cyano-*N*-(3-cyano-4-methoxybenzyl)-2-fluorobenzamide (120 mg) and (*R*)-2-amino-1-butanol (69.2 mg) in a similar manner to Example 12-(2) as a colorless powder.
NMR (DMSO-d_6, δ): 0.89 (3H, t, J=7Hz), 1.36-1.58 (1H, br), 1.58-1.79

(1H, br), 3.38-3.55 (3H, br), 3.91 (3H, s), 4.39 (2H, d, J=7Hz), 4.87 (1H, br), 6.86 (1H, d, J=8Hz), 7.23 (1H, d, J=8Hz), 7.57-7.75 (3H, br), 8.07 (1H, s), 8.73 (1H, d, J=8Hz), 9.06 (1H, br)

Example 74

5-Cyano-*N*-(3-cyano-4-methoxybenzyl)-2-[(*S*)-1-(hydroxymethyl)-propylmino]benzamide (115 mg) was prepared from 5-cyano-*N*-(3-cyano-4-methoxybenzyl)-2-fluorobenzamide (120 mg) and (*S*)-2-amino-1-butanol (69.2 mg) in a similar manner to Example 12-(2) as a colorless powder.

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=7Hz), 1.37-1.55 (1H, br), 1.57-1.77 (1H, br), 3.38-3.53 (3H, br), 3.90 (3H, s), 4.37 (2H, d, J=7Hz), 4.85 (1H, t, J=7Hz), 6.85 (1H, d, J=8Hz), 7.23 (1H, d, J=8Hz), 7.57-7.71 (3H, m), 8.05 (1H, d, J=2Hz), 8.69 (1H, d, J=8Hz), 9.06 (1H, br)

Example 75

5-Cyano-*N*-(3-cyano-4-methoxybenzyl)-2-(1,1-dimethyl-2-hydroxyethylamino)benzamide (90.4 mg) was prepared from 5-cyano-*N*-(3-cyano-4-methoxybenzyl)-2-fluorobenzamide (150 mg) and 2-amino-2-methyl-1-propanol (130 mg) in a similar manner to Example 12-(2) as a colorless powder.

NMR (DMSO-d_6, δ): 1.29 (6H, s), 3.39 (2H, d, J=7Hz), 3.90 (3H, s), 4.36 (2H, d, J=7Hz), 5.10 (1H, t, J=7Hz), 7.00 (1H, d, J=8Hz), 7.23 (1H, d, J=8Hz), 7.55 (1H, dd, J=2, 8Hz), 7.63 (1H, dd, J=2, 8Hz), 7.68 (1H, d, J=2Hz), 8.01 (1H, d, J=2Hz), 8.87 (1H, s), 9.03 (1H, br)

Example 76

5-Cyano-*N*-(3-cyano-4-methoxybenzyl)-2-(*cis*-4-hydroxycyclohexyl-amino)benzamide (98.7 mg) was prepared from 5-cyano-2-(*cis*-4-hydroxycyclohexylamino)benzoic acid (80.0 mg) and 3-cyano-4-methoxybenzylamine (59.8 mg) in a similar manner to Example 1-(3) as a colorless powder.

NMR (DMSO-d_6, δ): 1.43-1.70 (8H, br), 3.53-3.72 (2H, br), 3.90 (3H, s), 4.39 (2H, d, J=7Hz), 4.52 (1H, d, J=4Hz), 6.84 (1H, d, J=8Hz), 7.23 (1H, d, J=8Hz), 7.58-7.70 (3H, m), 8.08 (1H, d, J=2Hz), 8.83 (1H, d, J=8Hz), 9.07 (1H, br)

Example 77

5-Cyano-*N*-(3-cyano-4-methoxybenzyl)-2-(*trans*-4-hydroxycyclohexyl-amino)benzamide (121 mg) was prepared from 5-cyano-*N*-(3-cyano-4-methoxybenzyl)-2-fluorobenzamide (120 mg) and *trans*-4-aminocyclo-hexanol (89.4 mg) in a similar manner to Example 12-(2) as a colorless powder.

NMR (DMSO-d_6, δ): 1.15-1.40 (4H, br), 1.75-1.88 (2H, br), 1.88-2.00 (2H, br), 3.35-3.54 (2H, br), 3.90 (3H, s), 4.36 (2H, d, J=7Hz), 4.60 (1H, d, J=4Hz), 6.86 (1H, d, J=8Hz), 7.22 (1H, d, J=8Hz), 7.57-7.71 (3H, m), 8.07 (1H, d, J=2Hz), 8.60 (1H, d, J=8Hz), 9.06 (1H, br)

Example 78

(1) 2-(*trans*-4-Aminocyclohexylamino)-5-cyano-*N*-(3-cyano-4-methoxybenzyl)benzamide (205 mg) was prepared from 5-cyano-*N*-(3-cyano-4-methoxybenzyl)-2-fluorobenzamide (200 mg) and *trans*-1,4-diaminocyclohexane (222 mg) in a similar manner to Example 12-(2) as a pale yellow powder.

NMR (DMSO-d_6, δ): 1.10-1.45 (4H, br), 1.68-1.85 (2H, br), 1.85-2.10 (2H, br), 2.50-2.70 (1H, br), 3.28-3.45 (1H, br), 3.90 (3H, s), 4.37 (2H, d, J=7Hz), 6.85 (1H, d, J=8Hz), 7.23 (1H, d, J=8Hz), 7.57-7.77 (3H, m), 8.07 (1H, d, J=2Hz), 8.60 (1H, d, J=8Hz), 9.08 (1H, br)

(2) 5-Cyano-*N*-(3-cyano-4-methoxybenzyl)-2-(*trans*-4-formamidocyclo-hexylamino)benzamide (108 mg) was prepared from 2-(*trans*-4-aminocyclohexylamino)-5-cyano-*N*-(3-cyano-4-methoxybenzyl)-benzamide (120 mg) in a similar manner to Example 70-(2) as a colorless powder.

NMR (DMSO-d_6, δ): 1.20-1.47 (4H, br), 1.78-1.90 (2H, br), 1.92-2.05 (2H, br), 3.37-3.51 (1H, br), 3.57-3.72 (1H, br), 3.90 (3H, s), 4.36 (2H, d, J=7Hz), 6.89 (1H, d, J=8Hz), 7.23 (1H, d, J=8Hz), 7.58-7.70 (3H, m), 7.94 (1H, s), 8.03 (1H, br), 8.07 (1H, d, J=2Hz), 8.62 (1H, d, J=8Hz), 9.07 (1H, br)

Example 79

(1) 5-Cyano-2-fluoro-*N*-(3-fluoro-4-methoxybenzyl)benzamide (2.48 g) was prepared from 5-cyano-2-fluorobenzoic acid (1.50 g) and 3-fluoro-4-methoxybenzylamine (1.55 g) in a similar manner to Example 1-(3) as

a colorless powder.
NMR (DMSO-d_6, δ): 3.82 (3H, s), 4.40 (2H, d, J=7Hz), 7.10-7.23 (3H, m), 7.56 (1H, m), 8.06 (1H, m), 8.26 (1H, m), 9.07 (1H, br)

(2) (*R*)-5-Cyano-*N*-(3-fluoro-4-methoxybenzyl)-2-[1-(hydroxymethyl)-ethylamino]benzamide (163 mg) was prepared from 5-cyano-2-fluoro-*N*-(3-fluoro-4-methoxybenzyl)benzamide (150 mg) and (*R*)-2-amino-1-propanol (74.5 mg) in a similar manner to Example 12-(2) as a colorless powder.
NMR (DMSO-d_6, δ): 1.13 (3H, d, J=7Hz), 3.42 (2H, t, J=7Hz), 3.61-3.73 (1H, br), 3.81 (3H, s), 4.34 (2H, d, J=7Hz), 4.92 (1H, t, J=7Hz), 6.85 (1H, d, J=8Hz), 7.06-7.21 (3H, m), 7.61 (1H, dd, J=2, 8Hz), 8.05 (1H, d, J=2Hz), 8.73 (1H, d, J=8Hz), 9.03 (1H, br)

Example 80

5-Cyano-*N*-(3-fluoro-4-methoxybenzyl)-2-[(*S*)-1-(hydroxymethyl)ethyl-amino]benzamide (152 mg) was prepared from 5-cyano-2-fluoro-*N*-(3-fluoro-4-methoxybenzyl)benzamide (150 mg) and (*S*)-2-amino-1-propanol (74.5 mg) in a similar manner to Example 12-(2) as a colorless powder.
NMR (DMSO-d_6, δ): 1.13 (3H, d, J=7Hz), 3.42 (2H, t, J=7Hz), 3.60-3.73 (1H, br), 3.81 (3H, s), 4.34 (2H, d, J=7Hz), 4.92 (1H, t, J=7Hz), 6.85 (1H, d, J=8Hz), 7.08-7.21 (3H, m), 7.60 (1H, dd, J=2, 8Hz), 8.05 (1H, d, J=2Hz), 8.72 (1H, d, J=8Hz), 9.04 (1H, br)

Example 81

5-Cyano-*N*-(3-fluoro-4-methoxybenzyl)-2-[(*R*)-1-(hydroxymethyl)-propylamino]benzamide (155 mg) was prepared from 5-cyano-2-fluoro-*N*-(3-fluoro-4-methoxybenzyl)benzamide (150 mg) and (*R*)-2-amino-1-butanol (88.5 mg) in a similar manner to Example 12-(2) as a colorless powder.
NMR (DMSO-d_6, δ): 0.88 (3H, t, J=7Hz), 1.38-1.52 (1H, br), 1.58-1.75 (1H, br), 3.38-3.53 (3H, br), 3.81 (3H, s), 4.34 (2H, d, J=7Hz), 4.85 (1H, t, J=7Hz), 6.85 (1H, d, J=8Hz), 7.08-7.21 (3H, m), 7.59 (1H, dd, J=2, 8Hz), 8.05 (1H, d, J=2Hz), 8.73 (1H, d, J=8Hz), 9.04 (1H, br)

Example 82

5-Cyano-*N*-(3-fluoro-4-methoxybenzyl)-2-[(*S*)-1-(hydroxymethyl)-propylamino]benzamide (135 mg) was prepared from 5-cyano-2-fluoro-*N*-(3-fluoro-4-methoxybenzyl)benzamide (150 mg) and (*S*)-2-amino-1-butanol (88.5 mg) in a similar manner to Example 12-(2) as a colorless powder.

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=7Hz), 1.36-1.52 (1H, br), 1.58-1.75 (1H, br), 3.38-3.54 (3H, br), 3.81 (3H, s), 4.34 (2H, d, J=7Hz), 4.85 (1H, t, J=7Hz), 6.85 (1H, d, J=8Hz), 7.07-7.21 (3H, m), 7.59 (1H, dd, J=2, 8Hz), 8.05 (1H, d, J=2Hz), 8.72 (1H, d, J=8Hz), 9.04 (1H, br)

Example 83

5-Cyano-2-(1,1-dimethyl-2-hydroxyethyl)amino-*N*-(3-fluoro-4-methoxybenzyl)benzamide (93.5 mg) was prepared from 5-cyano-2-fluoro-*N*-(3-fluoro-4-methoxybenzyl)benzamide (200 mg) and 2-amino-2-methyl-1-propanol (177 mg) in a similar manner to Example 12-(2) as a colorless powder.

NMR (DMSO-d_6, δ): 1.29 (6H, s), 3.39 (2H, d, J=7Hz), 3.81 (3H, s), 4.33 (2H, d, J=7Hz), 5.11 (1H, t, J=7Hz), 7.00 (1H, d, J=8Hz), 7.06-7.21 (3H, m), 7.54 (1H, dd, J=2, 8Hz), 8.00 (1H, d, J=2Hz), 8.89 (1H, s), 9.00 (1H, br)

Example 84

5-Cyano-*N*-(3-fluoro-4-methoxybenzyl)-2-(*cis*-4-hydroxycyclohexylamino)benzamide (91.3 mg) was prepared from 5-cyano-2-(*cis*-4-hydroxycyclohexylamino)benzoic acid (80.0 mg) and 3-fluoro-4-methoxybenzylamine (57.2 mg) in a similar manner to Example 1-(3) as a colorless powder.

NMR (DMSO-d_6, δ): 1.43-1.72 (8H, br), 3.52-3.71 (2H, br), 3.81 (3H, s), 4.36 (2H, d, J=7Hz), 4.52 (1H, d, J=4Hz), 6.84 (1H, d, J=8Hz), 7.07-7.22 (3H, m), 7.60 (1H, dd, J=2, 8Hz), 8.08 (1H, d, J=2Hz), 8.87 (1H, d, J=8Hz), 9.08 (1H, br)

Example 85

5-Cyano-*N*-(3-fluoro-4-methoxybenzyl)-2-(*trans*-4-hydroxy-cyclohexylamino)benzamide (189 mg) was prepared from 5-cyano-2-fluoro-*N*-(3-fluoro-4-methoxybenzyl)benzamide (150 mg) and *trans*-4-aminocyclohexanol (114 mg) in a similar manner to Example 12-(2) as a

colorless powder.
NMR (DMSO-d_6, δ): 1.14-1.40 (4H, br), 1.75-1.86 (2H, br), 1.88-2.02 (2H, br), 3.35-3.55 (2H, br), 3.81 (3H, s), 4.33 (2H, d, J=7Hz), 4.60 (1H, d, J=4Hz), 6.85 (1H, d, J=8Hz), 7.07-7.21 (3H, m), 7.60 (1H, dd, J=2, 8Hz), 8.06 (1H, d, J=2Hz), 8.64 (1H, d, J=8Hz), 9.06 (1H, br)

Example 86

(1) 2-(*trans*-4-Aminocyclohexylamino)-5-cyano-*N*-(3-fluoro-4-methoxybenzyl)benzamide (222 mg) was prepared from 5-cyano-2-fluoro-*N*-(3-fluoro-4-methoxybenzyl)benzamide (200 mg) and *trans*-1,4-diaminocyclohexane (227 mg) in a similar manner to Example 12-(2) as a colorless powder.
NMR (DMSO-d_6, δ): 1.10-1.30 (4H, br), 1.70-1.90 (2H, br), 1.90-2.03 (2H, br), 2.55-2.65 (1H, br), 3.25-3.45 (1H, br), 3.81 (3H, s), 4.33 (2H, d, J=7Hz), 6.84 (1H, d, J=8Hz), 7.06-7.21 (3H, m), 7.60 (1H, dd, J=2, 8Hz), 8.06 (1H, d, J=2Hz), 8.62 (1H, d, J=8Hz), 9.04 (1H, br)

(2) 5-Cyano-*N*-(3-fluoro-4-methoxybenzyl)-2-(*trans*-4-formamidocyclohexylamino)benzamide (125 mg) was prepared from 2-(*trans*-4-aminocyclohexylamino)-5-cyano-*N*-(3-fluoro-4-methoxybenzyl)-benzamide (120 mg) in a similar manner to Example 70-(2) as a colorless powder.
NMR (DMSO-d_6, δ): 1.18-1.50 (4H, br), 1.75-1.89 (2H, br), 1.93-2.04 (2H, br), 3.35-3.50 (1H, br), 3.55-3.73 (1H, br), 3.81 (3H, s), 4.34 (2H, d, J=7Hz), 6.89 (1H, d, J=8Hz), 7.07-7.21 (3H, m), 7.62 (1H, d, J=8Hz), 7.94 (1H, s), 8.04 (1H, br), 8.07 (1H, s), 8.65 (1H, d, J=8Hz), 9.06 (1H, br)

Example 87

5-Cyano-*N*-(3-cyano-4-methoxybenzyl)-2-(*c*-3,*c*-4-dihydroxy-*r*-1-cyclohexylamino)benzamide (170 mg) was prepared from 5-cyano-*N*-(3-cyano-4-methoxybenzyl)-2-fluorobenzamide (140 mg) and *c*-4-amino-r-1,c-2-cyclohexanediol (65 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 1.38-1.84 (6H, m), 3.43-3.59 (2H, m), 3.68 (1H, m), 3.90 (3H, s), 4.30-4.38 (3H, m), 4.53 (1H, d, J=6Hz), 6.86 (1H, d, J=9Hz), 7.23 (1H, d, J=8Hz), 7.56-7.67 (3H, m), 8.05 (1H, d, J=2Hz), 8.64 (1H, d, J=7Hz), 9.03 (1H, t, J=6Hz)

Example 88

5-Cyano-*N*-(3-cyano-4-methoxybenzyl)-2-(*t*-3,*t*-4-dihydroxy-*r*-1-cyclopentylamino)benzamide (204 mg) was prepared from 5-cyano-*N*-(3-cyano-4-methoxybenzyl)-2-fluorobenzamide (192 mg) and *t*-4-amino-r-1,*c*-2-cyclopentanediol (80 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 1.56 (2H, m), 2.10 (2H, m), 3.90 (3H, s), 3.93-4.08 (3H, m), 4.37 (2H, d, J=6Hz), 4.55 (1H, d, J=4Hz), 6.71 (1H, d, J=9Hz), 7.23 (1H, d, J=8Hz), 7.58-7.67 (3H, m), 8.07 (1H, d, J=2Hz), 8.64 (1H, d, J=7Hz), 9.08 (1H, t, J=6Hz)

Example 89

5-Cyano-*N*-(3-cyano-4-methoxybenzyl)-2-(*t*-3,*t*-4-dihydroxy-*r*-1-cyclohexylamino)benzamide (143 mg) was prepared from 5-cyano-*N*-(3-cyano-4-methoxybenzyl)-2-fluorobenzamide (130 mg) and *t*-4-amino-r-1,*c*-2-cyclohexanediol (61 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 1.26 (1H, m), 1.41 (1H, m), 1.53 (1H, m), 1.71 (1H, m), 1.82-2.02 (2H, m), 3.52 (1H, m), 3.68-3.79 (2H, m), 3.90 (3H, s), 4.37 (2H, d, J=6Hz), 4.45 (1H, d, J=5Hz), 4.50 (1H, d, J=4Hz), 6.79 (1H, d, J=9Hz), 7.22 (1H, d, J=9Hz), 7.59-7.68 (3H, m), 8.07 (1H, d, J=2Hz), 8.63 (1H, d, J=7Hz), 9.06 (1H, t, J=6Hz)

Example 90

5-Cyano-*N*-(3-cyano-4-methoxybenzyl)-2-[2-hydroxy-1-(hydroxymethyl)ethylamino]benzamide (124 mg) was prepared from 5-cyano-*N*-(3-cyano-4-methoxybenzyl)-2-fluorobenzamide (130 mg) and 2-amino-1,3-propanediol (61 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 3.42-3.60 (4H m), 3.90 (3H, s), 4.36 (2H, d, J=6Hz), 4.86 (2H, m), 6.88 (1H, d, J=9Hz), 7.22 (1H, d, J=9Hz), 7.57-7.67 (3H, m), 8.05 (1H, d, J=2Hz), 8.82 (1H, d, J=6Hz), 9.02 (1H, t, J=6Hz)

Example 91

(1) To a solution of (1*S*,2*R*,4*R*)-4-(4-toluenesulfonyloxy)-1,2-cyclohexylidenedioxycyclohexane (174 mg) in dioxane (4 ml) was added 1*N*-hydrochloric acid (1 ml), and the mixture was stirred for 1.5 hours at 35°C. The resulting mixture was evaporated *in vacuo* and the residue was chromatographed on silica gel eluting with a mixture of n-hexane and ethyl acetate (1:2) to give (1*S*,2*R*,4*R*)-4-(4-toluenesulfonyloxy)cyclo-

hexane-1,2-diol (134 mg).
NMR ($CDCl_3$, δ): 1.43 (1H, m), 1.66 (1H, m), 1.77-2.00 (4H, m), 2.46 (3H, s), 3.62 (1H, m), 3.78 (1H, m), 4.48 (1H, m), 7.35 (1H, d, J=8Hz), 7.80 (1H, d, J=8Hz)

(2) To a solution of (1*S*,2*R*,4*R*)-4-(4-toluenesulfonyloxy)cyclohexane-1,2-diol (128 mg) in toluene (3 ml) was added 1,1'-thiocarbonyldi-imidazole (119 mg), and the mixture was stirred for 1 hour at 80°C. The resulting mixture was evaporated *in vacuo* and the residue was chromatographed on silica gel eluting with a mixture of n-hexane and ethyl acetate (1:2) to give (1*S*,2*R*,4*R*)-4-(4-toluenesulfonyloxy)-1,2-thiocarbonyldioxycyclohexane (125 mg).
NMR ($CDCl_3$, δ): 1.76-1.93 (3H, m), 2.00 (1H, m), 2.23-2.34 (2H, m), 2.46 (3H, s), 4.64 (1H, m), 4.80-4.94 (2H, m), 7.36 (1H, d, J=8Hz), 7.80 (1H, d, J=8Hz)

(3) To a solution of (1*S*,2*R*,4*R*)-4-(4-toluenesulfonyloxy)-1,2-thiocarbonyldioxycyclohexane (120 mg) in toluene (1.5 ml) was added 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (213 mg), and the mixture was stirred for 2 hours at 50°C. The resulting mixture was evaporated *in vacuo* and the residue was chromatographed on silica gel eluting with a mixture of n-hexane and ethyl acetate (2:1) to give (*R*)-1-(4-toluenesulfonyloxy)-3-cyclohexene (23 mg).
NMR ($CDCl_3$, δ): 1.73-1.93 (2H, m), 1.98-2.35 (4H, m), 2.45 (3H, s), 4.74 (1H, m), 5.47 (1H, m), 5.65 (1H, m), 7.34 (1H, d, J=8Hz), 7.81 (1H, d, J=8Hz)

(4) To a solution of (*R*)-1-(4-toluenesulfonyloxy)-3-cyclohexene (20 mg) in tetrahydrofuran (2 ml) and water (0.1 ml) was added *N*-methylmorpholine *N*-oxide (19 mg) and osmium tetroxide (0.1 ml of 4% solution in water), and the mixture was stirred for 1 hour at ambient temperature. The resulting mixture was evaporated *in vacuo*, diluted with ethyl acetate and washed with 1*N*-hydrochloric acid, a sodium hydrogen carbonate solution and brine successively. The organic layer was dried over sodium sulfate and evaporated *in vacuo*, and the residue was chromatographed on silica gel eluting with a mixture of n-hexane and ethyl acetate (1:2) to give (1*R*,2*S*,4*R*)-4-(4-toluene-sulfonyloxy)-

cyclohexane-1,2-diol (23 mg).
Mass (m/z): 309 (M+Na)

(5) To a solution of (1*R*,2*S*,4*R*)-4-(4-toluenesulfonyloxy)cyclohexane-1,2-diol (23 mg) in dichloromethane (2 ml) were added 1,1-dimethoxy-cyclohexane (0.037 ml) and *p*-toluenesulfonic acid (5 mg), and the mixture was stirred for 1 hour at ambient temperature. The resulting mixture was evaporated *in vacuo*, diluted with ethyl acetate and washed with sodium hydrogen carbonate solution and brine successively. The organic layer was dried over sodium sulfate and evaporated *in vacuo*, and the residue was chromatographed on silica gel eluting with a mixture of n-hexane and ethyl acetate (4:1) to give (1*R*,2*S*,4*R*)-4-(4-toluenesulfonyl-oxy)-1,2-cyclohexylidenedioxycyclohexane (15.7 mg).
NMR ($CDCl_3$, δ): 1.33-1.43 (2H, m), 1.47-1.68 (10H, m), 1.74-1.99 (4H, m), 2.45 (3H, s), 4.14 (1H, q, J=5Hz), 4.23 (1H, q, J=5Hz), 4.78 (1H, m), 7.34 (2H, d, J=8Hz), 7.79 (2H, d, J=8Hz)

(6) (1*R*,2*S*,4*S*)-4-Azido-1,2-cyclohexylidenedioxycyclohexane (8 mg) was prepared from (1*R*,2*S*,4*R*)-4-(4-toluenesulfonyloxy)-1,2-cyclohexylidenedioxycyclohexane (15 mg) and sodium azide (11 mg) in a similar manner to Example 34-(2).
NMR ($CDCl_3$, δ): 1.34-1.50 (2H, m), 1.50-1.83 (12H, m), 2.08-2.29 (2H, m), 3.25 (1H, m), 4.08-4.17 (2H, m)

(7) (1*R*,2*S*,4*S*)-4-Amino-1,2-cyclohexylidenedioxycyclohexane (7 mg) was prepared from (1*R*,2*S*,4*S*)-4-azido-1,2-cyclohexylidenedioxy-cyclohexane (8 mg) in a similar manner to Example 29-(3).
NMR ($CDCl_3$, δ): 1.33-1.85 (14H, m), 1.94-2.18 (2H, m), 2.68 (1H, m), 4.08-4.20 (2H, m)

(8) *N*-(3-Chloro-4-methoxybenzyl)-5-cyano-2-[(1*S*,3*S*,4*R*)-3,4-cyclohexylidenedioxycyclohexylamino]benzamide (134 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-5-cyano-2-fluorobenzamide (100 mg) and (1*R*,2*S*,4*S*)-4-amino-1,2-cyclohexylidenedioxycyclohexane (66 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 1.26-1.90 (15H, m), 2.04 (1H, m), 3.58 (1H, m), 3.83 (3H, s), 4.09 (1H, m), 4.19 (1H, m), 4.34 (2H, d, J=6Hz), 6.84 (1H, d,

J=9Hz), 7.10 (1H, d, J=9Hz), 7.24 (1H, dd, J=2, 9Hz), 7.35 (1H, d, J=2Hz), 7.59 (1H, dd, J=2, 9Hz), 8.03 (1H, d, J=2Hz), 8.71 (1H, d, J=7Hz), 9.01 (1H, t, J=6Hz)

(9) *N*-(3-Chloro-4-methoxybenzyl)-5-cyano-2-[(1*S*,3*S*,4*R*)-3,4-dihydroxycyclohexylamino]benzamide (71 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-5-cyano-2-[(1*S*,3*S*,4*R*)-3, 4-cyclohexylidenedioxycyclohexylamino]benzamide (130 mg) in a similar manner to Example 55-(5).

NMR (DMSO-d_6, δ): 1.38-1.84 (6H, m), 3.43-3.58 (2H, m), 3.68 (1H, m), 3.83 (3H, s), 4.28-4.38 (3H, m), 4.53 (1H, d, J=5Hz), 6.86 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.27 (1H, dd, J=2, 9Hz), 7.37 (1H, d, J=2Hz), 7.60 (1H, dd, J=2, 9Hz), 8.03 (1H, d, J=2Hz), 8.67 (1H, d, J=7Hz), 9.02 (1H, t, J=5Hz)

Example 92

(1) *N*-(3-Cyano-4-methoxybenzyl)-2-fluoro-5-(trifluoromethyl)-benzamide (1.5 g) was prepared from 2-fluoro-5-(trifluoromethyl)benzoic acid (1.2 g) and 3-cyano-4-methoxybenzylamine (1.0 g) in a similar manner to Example 1-(3) as a white powder.

NMR ($CDCl_3$, δ): 3.93 (3H, s), 4.62 (2H, d, J=5Hz), 6.96 (1H, d, J=8Hz), 7.09 (1H, br), 7.23-7.32 (1H, m), 7.53-7.61 (2H, m), 7.72-7.81 (1H, m), 8.45 (1H, dd, J=8, 2Hz)

(2) *N*-(3-Cyano-4-methoxybenzyl)-2-(*t*-3,*t*-5-dihydroxy-*r*-1-cyclohexylamino)-5-trifluoromethylbenzamide (180 mg) was prepared from *N*-(3-cyano-4-methoxybenzyl)-2-fluoro-5-trifluoromethylbenzamide (240 mg) and *t*-5-amino-*r*-1,*c*-3-cyclohexanediol (112 mg) in a similar manner to Example 12-(2).

NMR (DMSO-d_6, δ): 1.20 (1H, m), 1.40 (2H, m), 1.86 (2H, m), 2.04 (1H, m), 3.65 (2H, m), 3.90 (3H, s), 4.02 (1H, m), 4.40 (2H, d, J=6Hz), 4.72 (2H, d, J=5Hz), 6.87 (1H, d, J=9Hz), 7.23 (1H, d, J=9Hz), 7.53-7.67 (3H, m), 7.98 (1H, d, J=2Hz), 8.65 (1H, d, J=7Hz), 9.16 (1H, t, J=6Hz)

Example 93

N-(3-Cyano-4-methoxybenzyl)-2-[2-hydroxy-1-(hydroxymethyl)-ethylamino]-5-trifluoromethylbenzamide (180 mg) was prepared from

N-(3-cyano-4-methoxybenzyl)-2-fluoro-5-trifluoromethylbenzamide (172 mg) and 2-amino-1,3-propanediol (133 mg) in a similar manner to Example 12-(2).

NMR (DMSO-d_6, δ): 3.50 (4H, m), 3.90 (3H, s), 4.38 (2H, d, J=6Hz), 4.82 (2H, m), 6.91 (1H, d, J=9Hz), 7.23 (1H, d, J=9Hz), 7.53 (1H, dd, J=2, 9Hz), 7.59-7.67 (2H, m), 7.93 (1H, d, J=2Hz), 8.63 (1H, m), 9.08 (1H, t, J=6Hz)

Example 94

(1) *N*-(3-Chloro-4-methoxybenzyl)-2-[(1*S*,3*S*,4*R*)-3,4-cyclohexylidene-dioxycyclohexylamino]-5-trifluoromethylbenzamide (183 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-2-fluoro-5-trifluoromethyl-benzamide (120 mg) and (1*R*,2*S*,4*S*)-4-amino-1,2-cyclohexylidenedioxy-cyclohexane (107 mg) in a similar manner to Example 12-(2).

NMR (DMSO-d_6, δ): 1.32 (2H, m), 1.50-1.95 (13H, m), 2.05 (1H, m), 3.54 (1H, m), 3.83 (3H, s), 4.10 (1H, m), 4.18 (1H, m), 4.35 (2H, d, J=6Hz), 6.86 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.24 (1H, dd, J=2, 9Hz), 7.35 (1H, d, J=2Hz), 7.52 (1H, dd, J=2, 9Hz), 7.92 (1H, d, J=2Hz), 8.50 (1H, d, J=7Hz), 9.06 (1H, t, J=6Hz)

(2) *N*-(3-Chloro-4-methoxybenzyl)-2-[(1*S*,3*S*,4*R*)-3,4-dihydroxycyclo-hexylamino]-5-trifluoromethylbenzamide (91 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-2-[(1*S*,3*S*,4*R*)-3,4-cyclohexylidenedioxy-cyclohexylamino]-5-trifluoromethylbenzamide (148 mg) in a similar manner to Example 55-(5).

NMR (DMSO-d_6, δ): 1.37-1.87 (6H, m), 3.41-3.59 (2H, m), 3.69 (1H, m), 3.83 (3H, s), 4.30 (1H, d, J=4Hz), 4.36 (1H, d, J=6Hz), 4.52 (1H, d, J=6Hz), 6.88 (1H, d, J=9Hz), 7.12 (1H, d, J=9Hz), 7.27 (1H, dd, J=2, 9Hz), 7.37 (1H, d, J=2Hz), 7.52 (1H, dd, J=2, 9Hz), 7.92 (1H, d, J=2Hz), 8.44 (1H, d, J=7Hz), 9.09 (1H, t, J=6Hz)

Example 95

(1) To a solution of (1*S*,2*R*,4*R*)-4-amino-1,2-cyclohexylidenedioxy-cyclohexane (988 mg) in methanol (20 ml) were added triethylamine (0.85 ml) and benzyl chloroformate (0.77 ml), and the mixture was stirred for 1 hour at ambient temperature. The solvent was evaporated *in vacuo*, and the residue was diluted with ethyl acetate and washed with

a sodium hydrogen carbonate solution and brine successively. The organic layer was dried over sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a mixture of n-hexane and ethyl acetate (2:1) to give benzyl (1*R*,3*R*,4*S*)-3,4-cyclohexylidenedioxy-cyclohexylcarbamate(1.37 g).
NMR ($CDCl_3$, δ): 1.33-1.44 (2H, m), 1.52-2.08 (14H, m), 3.73 (1H, m), 4.07-4.24 (2H, m), 5.04-5.14 (2H, m), 5.34 (1H, m), 7.27-7.39 (5H, m)

(2) Benzyl (1*R*,3*R*,4*S*)-3,4-dihydroxycyclohexylcarbamate (802 mg) was prepared from benzyl (1*R*,3*R*,4*S*)-3,4-cyclohexylidenedioxycyclohexyl-carbamate (1.37 g) in a similar manner to Example 91-(1).
NMR ($CDCl_3$, δ): 1.46-2.02 (5H, m), 2.31 (1H, m), 3.68-3.80 (2H, m), 3.89 (1H, m), 5.05-5.13 (2H, m), 5.64 (1H, m), 7.26-7.38 (5H, m)

(3) Benzyl (1*R*,3*R*,4*S*)-3,4-thiocarbonyldioxycyclohexylcarbamate (434 mg) was prepared from benzyl (1*R*,3*R*,4*S*)-3,4-dihydroxycyclohexyl-carbamate (416 mg) in a similar manner to Example 91-(2).
NMR ($CDCl_3$, δ): 1.46-1.72 (2H, m), 1.78-1.96 (2H, m), 2.26-2.46 (2H, m), 3.68 (1H, m), 4.76-5.01 (3H, m), 5.09 (2H, m), 7.27-7.40 (5H, m)

(4) Benzyl (*R*)-3-cyclohexenylcarbamate (195 mg) was prepared from benzyl (1*R*,3*R*,4*S*)-3,4-thiocarbonyldioxycyclohexylcarbamate (434 mg), in a similar manner to Example 91-(3).
NMR ($CDCl_3$, δ): 1.58 (1H, m), 1.82-1.95 (2H, m), 2.06-2.37 (2H, m), 2.40 (1H, m), 3.87 (1H, m), 4.78 (1H, m), 5.54-5.72 (2H, m), 7.27-7.38 (5H, m)

(5) Benzyl (1*R*,3*S*,4*R*)-3,4-dihydroxycyclohexylcarbamate (83 mg) was prepared from benzyl (*R*)-3-cyclohexenylcarbamate (192 mg) in a similar manner to Example 91-(4).
NMR (DMSO-d_6, δ): 1.15 (1H, m), 1.34 (1H, m), 1.44-1.83 (4H, m), 3.35 (1H, m), 3.64 (1H, m), 3.74 (1H, m), 4.28 (1H, m), 4.34 (1H, m), 4.98 (2H, s), 7.08 (1H, d, J=7Hz), 7.26-7.41 (5H, m)

(6) (1*R*,2*S*,4*R*)-4-Amino-1,2-cyclohexanediol (40 mg) was prepared from benzyl (1*R*,3*S*,4*R*)-3,4-dihydroxycyclohexylcarbamate (83 mg) in a similar manner to Example 29-(3).

NMR ($CDCl_3$, δ): 1.06-1.34 (2H, m), 1.65-1.66 (2H, m), 1.84 (1H, m), 2.04 (1H, m), 3.07 (1H, m), 3.58 (1H, m), 3.96 (1H, m)

(7) *N*-(3-Chloro-4-methoxybenzyl)-5-cyanol-2-[(1*R*,3*S*,4*R*)-3,4-dihydroxycyclohexylamino]benzamide (69 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-5-cyano-2-fluorobenzamide (90 mg) and (1*R*,2*S*,4*R*)-4-amino-1,2-cyclohexanediol (41 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 1.26 (1H, m), 1.41 (1H, m), 1.53 (1H, m), 1.71 (1H, m), 1.82-2.02 (2H, m), 3.52 (1H, m), 3.66-3.80 (2H, m), 3.83 (3H, s), 4.34 (2H, d, J=5Hz), 4.44 (1H, d, J=5Hz), 4.49 (1H, d, J=3Hz), 6.79 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.26 (1H, dd, J=2, 9Hz), 7.37 (1H, d, J=2Hz), 7.63 (1H, dd, J=2, 9Hz), 8.05 (1H, d, J=2Hz), 8.65 (1H, d, J=8Hz), 9.05 (1H, t, J=5Hz)

Example 96

N-(3-Chloro-4-methoxybenzyl)-5-cyano-2-(*t*-4-hydroxy-*t*-3-methoxy-*r*-1-cyclopentylamino)benzamide (38 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-5-cyano-2-fluorobenzamide (65 mg) and *t*-4-amino-*c*-2-methoxy-*r*-1-cyclopentanol (26 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 1.49-1.63 (2H, m), 2.08-2.22 (2H, m), 3.28 (3H, s), 3.67 (1H, m), 3.83 (3H, s), 4.02 (1H, m), 4.14 (1H, m), 4.34 (2H, d, J=6Hz), 4.53 (1H, d, J=5Hz), 6.72 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.25 (1H, dd, J=2, 9Hz), 7.37 (1H, d, J=2Hz), 7.63 (1H, dd, J=2, 9Hz), 8.06 (1H, d, J=2Hz), 8.67 (1H, d, J=6Hz), 9.07 (1H, t, J=6Hz)

Example 97

(1) (1*S*,2*R*,4*R*)-4-Amino-1,2-cyclohexanediol (94 mg) was prepared from benzyl (1*R*,3*R*,4*S*)-3,4-dihydroxycyclohexylcarbamate (181 mg) in a similar manner to Example 29-(3).
NMR ($CDCl_3$, δ): 1.42-1.78 (7H, m), 1.91 (1H, m), 2.88 (1H; m), 3.68 (1H, m), 3.75 (1H, m)

(2) *N*-(3-Chloro-4-methoxybenzyl)-2-[(1*R*,3*R*,4*S*)-3,4-dihydroxycyclohexylamino]-5-trifluoromethylbenzamide (79 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-2-fluoro-5-trifluoromethylbenzamide (122

mg) and (1*S*,2*R*,4*R*)-4-amino-1,2-cyclohexanediol (49 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 1.37-1.87 (6H, m), 3.41-3.59 (2H, m), 3.69 (1H, m), 3.83 (3H, s), 4.30 (1H, d, J=3Hz), 4.36 (1H, d, J=6Hz), 4.52 (1H, d, J=5Hz), 6.88 (1H, d, J=9Hz), 7.12 (1H, d, J=9Hz), 7.27 (1H, dd, J=2, 9Hz), 7.37 (1H, d, J=2Hz), 7.52 (1H, dd, J=2, 9Hz), 7.92 (1H, d, J=2Hz), 8.44 (1H, d, J=7Hz), 9.08 (1H, t, J=6Hz)

Example 98

N-(4-Chloro-3-methoxybenzyl)-5-cyano-2-[(1*R*,3*R*,4*S*)-3,4-dihydroxycyclohexylamino]benzamide (104 mg) was prepared from *N*-(4-chloro-3-methoxybenzyl)-5-cyano-2-fluorobenzamide (122 mg) and (1*S*,2*R*,4*R*)-4-amino-1,2-cyclohexanediol (49 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 1.38-1.84 (6H, m), 3.43-3.58 (2H, m), 3.68 (1H, m), 3.85 (3H, s), 4.32 (1H, d, J=3Hz), 4.41 (2H, d, J=5Hz), 4.54 (1H, d, J=5Hz), 6.86 (1H, d, J=9Hz), 6.90 (1H, dd, J=2, 9Hz), 7.11 (1H, d, J=2Hz), 7.37 (1H, d, J=8Hz), 7.61 (1H, dd, J=2, 9Hz), 8.05 (1H, d, J=2Hz), 8.63 (1H, d, J=7Hz), 9.06 (1H, t, J=5Hz)

Example 99

(1) *c*-3-Methoxy-*c*-5-(*p*-toluenesulfonyloxy)-*r*-1-cyclohexanol (115 mg) was prepared from *c*-5-(*p*-toluenesulfonyloxy)-*r*-1,*c*-3-cyclohexanediol (240 mg) in a similar manner to Example 105-(1).
NMR ($CDCl_3$, δ): 1.28 (1H, q, J=12Hz), 1.53 (2H, m), 2.13-2.33 (3H, m), 2.46 (3H, s), 3.19 (1H, m), 3.32 (3H, s), 3.59 (1H, m), 4.44 (1H, m), 7.35 (2H, d, J=8Hz), 7.80 (2H, d, J=8Hz)

(2) *t*-5-Azido-*c*-3-methoxy-*r*-1-cyclohexanol (67 mg) was prepared from *c*-3-methoxy-*c*-5-(*p*-toluenesulfonyloxy)-*r*-1-cyclohexanol (112 mg) and sodium azide (63 mg) in a similar manner to Example 34-(2).
NMR ($CDCl_3$, δ): 1.50-1.75 (3H, m), 1.88 (1H, m), 2.08-2.24 (2H, m), 3.38 (3H, s), 3.74 (1H, m), 3.95 (1H, m), 4.10 (1H, m)

(3) *t*-5-Amino-*c*-3-methoxy-*r*-1-cyclohexanol (28 mg) was prepared from *t*-5-azido-*c*-3-methoxy-*r*-1-cyclohexanol (64 mg) in a similar manner to Example 29-(3).

NMR ($CDCl_3$, δ): 1.17-1.36 (2H, m), 1.57 (1H, m), 2.03-2.12 (2H, m), 2.19 (1H, m), 3.36 (3H, s), 3.47 (1H, m), 3.75 (1H, m), 4.07 (1H, m)

(4) *N*-(3-Chloro-4-methoxybenzyl)-5-cyano-2-(t-5-hydroxy-t-3-methoxy-*r*-1-cyclohexylamino)benzamide (37 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-5-cyano-2-fluorobenzamide (57 mg) and *t*-5-amino-c-3-methoxy-*r*-1-cyclohexanol (28 mg) in a similar manner to Example 12-(2).

NMR (DMSO-d_6, δ): 1.06 (1H, m), 1.42 (2H, m), 1.87 (1H, m), 1.97 (1H, m), 2.22 (1H, m), 3.19 (3H, s), 3.29 (1H, m), 3.65 (1H, m), 3.83 (3H, s), 4.06 (1H, m), 4.37 (2H, d, J=6Hz), 4.74 (1H, d, J=5Hz), 6.85 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.26 (1H, dd, J=2, 9Hz), 7.37 (1H, dd, J=2, 9Hz), 7.38 (1H, d, J=2Hz), 7.64 (1H, dd, J=2, 9Hz), 8.08 (1H, d, J=2Hz), 8.83 (1H, d, J=8Hz), 9.08 (1H, t, J=6Hz)

Example 100

N-(4-Chloro-3-methoxybenzyl)-5-cyano-2-(*t*-3,*t*-4-dihydroxy-*r*-1-cyclopentylamino)benzamide (97 mg) was prepared from *N*-(4-chloro-3-methoxybenzyl)-5-cyano-2-fluorobenzamide (110 mg) and *t*-4-amino-*r*-1,*c*-2-cyclopentanediol (44 mg) in a similar manner to Example 12-(2).

NMR (DMSO-d_6, δ): 1.55 (2H, m), 2.10 (2H, m), 3.85 (3H, s), 3.93-4.09 (3H, m), 4.41 (2H, d, J=6Hz), 4.54 (2H, d, J=4Hz), 6.71 (1H, d, J=9Hz), 6.90 (1H, dd, J=2, 8Hz), 7.11 (1H, d, J=9Hz), 7.37 (1H, d, J=8Hz), 7.64 (1H, dd, J=2, 9Hz), 8.08 (1H, d, J=2Hz), 8.65 (1H, d, J=6Hz), 9.11 (1H, t, J=6Hz)

Example 101

5-Cyano-2-(*t*-5-hydroxy-*t*-3-methoxy-*r*-1-cyclohexylamino)-*N*-(3,4-dimethoxybenzyl)benzamide (57 mg) was prepared from 5-cyano-2-fluoro-*N*-(3,4-dimethoxybenzyl)benzamide (72 mg) and *t*-5-amino-*c*-3-methoxy-*r*-1-cyclohexanol (37 mg) in a similar manner to Example 12-(2).

NMR (DMSO-d_6, δ): 1.16 (1H, m), 1.43 (2H, m), 1.87 (1H, m), 1.98 (1H, m), 2.22 (1H, m), 3.20 (3H, s), 3.33 (1H, m), 3.65 (1H, m), 3.73 (3H, s), 3.74 (3H, s), 4.06 (1H, m), 4.36 (2H, d, J=6Hz), 4.75 (1H, d, J=4Hz), 6.81-6.97 (4H, m), 7.64 (1H, dd, J=2, 9Hz), 8.09 (1H, d, J=2Hz), 8.87 (1H, d, J=8Hz), 9.04 (1H, t, J=6Hz)

Example 102

N-(4-Chloro-3-methoxybenzyl)-5-cyano-2-(*t*-5-hydroxy-*t*-3-methoxy-*r*-1-cyclohexylamino)benzamide (66 mg) was prepared from *N*-(4-chloro-3-methoxybenzyl)-5-cyano-2-fluorobenzamide (125 mg) and *t*-5-amino-*c*-3-methoxy-*r*-1-cyclohexanol (57 mg) in a similar manner to Example 12-(2).

NMR (DMSO-d_6, δ): 1.16 (1H, m), 1.42 (2H, m), 1.87 (1H, m), 1.98 (1H, m), 2.20 (1H, m), 3.19 (3H, s), 3.32 (1H, m), 3.65 (1H, m), 3.85 (3H, s), 4.06 (1H, m), 4.43 (2H, d, J=6Hz), 4.74 (1H, d, J=4Hz), 6.85 (1H, d, J=9Hz), 6.89 (1H, dd, J=2, 8Hz), 7.13 (1H, d, J=2Hz), 7.37 (1H, d, J=8Hz), 7.65 (1H, dd, J=2, 9Hz), 8.11 (1H, d, J=2Hz), 8.84 (1H, d, J=7Hz), 9.13 (1H, t, J=6Hz)

Example 103

N-(4-Chloro-3-methoxybenzyl)-5-cyano-2-(*t*-3,*t*-5-dihydroxy-*r*-1-cyclohexylamino)benzamide (59 mg) was prepared from *N*-(4-chloro-3-methoxybenzyl)-5-cyano-2-fluorobenzamide (125 mg) and *t*-5-amino-*r*-1,*c*-3-cyclohexanediol (57 mg) in a similar manner to Example 12-(2).

NMR (DMSO-d_6, δ): 1.20 (1H, m), 1.41 (2H, m), 1.85 (2H, m), 2.03 (1H, m), 3.59-3.70 (2H, m), 3.85 (3H, s), 4.04 (1H, m), 4.43 (2H, d, J=5Hz), 4.75 (2H, d, J=5Hz), 6.85 (1H, d, J=9Hz), 6.89 (1H, dd, J=2, 8Hz), 7.12 (1H, d, J=2Hz), 7.37 (1H, d, J=8Hz), 7.65 (1H, dd, J=2, 9Hz), 8.10 (1H, d, J=2Hz), 8.86 (1H, d, J=7Hz), 9.13 (1H, t, J=5Hz)

Example 104

5-Cyano-N-(3-cyano-4-methoxybenzyl)-2-(*t*-3,*t*-5-dihydroxy-*r*-1-cyclohexylamino)benzamide (123 mg) was prepared from 5-cyano-N-(3-cyano-4-methoxybenzyl)-2-fluorobenzamide (130 mg) and *t*-5-amino-*r*-1,*c*-3-cyclohexanediol (61 mg) in a similar manner to Example 12-(2).

NMR (DMSO-d_6, δ): 1.26 (1H, m), 1.41 (1H, m), 1.53 (1H, m), 1.71 (1H, m), 1.82-2.02 (2H, m), 3.52 (1H, m), 3.68-3.79 (2H, m), 3.90 (3H, s), 4.37 (2H, d, J=6Hz), 4.45 (1H, d, J=5Hz), 4.50 (1H, d, J=4Hz), 6.79 (1H, d, J=9Hz), 7.22 (1H, d, J=9Hz), 7.59-7.68 (3H, m), 8.07 (1H, d, J=2Hz), 8.63 (1H, d, J=7Hz), 9.06 (1H, t, J=6Hz)

Example 105

(1) To a solution of benzyl *N*-(*t*-3,*t*-4-dihydroxy-*r*-1-cyclopentyl)-carbamate (134 mg) in 1,2-dichloroethane (3 ml) were added 2,6-di-*tert*-butyl-4-methylphenol (142 mg) and trimethyloxonium tetrafluoroborate (87 mg), and the mixture was refluxed for 1.5 hours. The resulting mixture was diluted with diethyl ether and washed successively with 1*N*-hydrochloric acid and brine. The organic layer was dried over sodium sulfate, evaporated *in vacuo* and chromatographed on silica gel eluting with a mixture of chloroform and methanol (9:1) to give benzyl *N*-(*t*-3-hydroxy-*t*-4-methoxy-*r*-1-cyclopentyl)carbamate (68 mg).
NMR ($CDCl_3$, δ): 1.61-1.79 (2H, m), 2.14-2.28 (2H, m), 3.38 (3H, s), 3.80 (1H, m), 4.18-4.33 (2H, m), 4.74 (1H, m), 5.09 (2H, brs), 7.25-7.42 (5H, m)

(2) *t*-4-Amino-*c*-2-methoxy-*r*-1-cyclopentanol (26 mg) was prepared from benzyl *N*-(*t*-3-hydroxy-*t*-4-methoxy-*r*-1-cyclopentyl)carbamate (65 mg) in a similar manner to Example 29-(3).
NMR ($CDCl_3$, δ): 1.45-1.70 (2H, m), 1.95-2.14 (2H, m), 3.39 (3H, s), 3.69 (1H, m), 3.85 (1H, m), 4.28 (1H, m)

(3) *N*-(4-Chloro-3-methoxybenzyl)-5-cyano-2-(*t*-4-hydroxy-*t*-3-methoxy-*r*-1-cyclopentylamino)benzamide (58 mg) was prepared from *N*-(4-chloro-3-methoxybenzyl)-5-cyano-2-fluorobenzamide (58 mg) and *t*-4-amino-*c*-2-methoxy-*r*-1-cyclopentanol (26 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 1.49-1.63 (2H, m), 2.08-2.24 (2H, m), 3.28 (3H, s), 3.66 (1H, m), 3.85 (3H, s), 4.02 (1H, m), 4.14 (1H, m), 4.41 (2H, d, J=6Hz), 4.53 (1H, d, J=4Hz), 6.72 (1H, d, J=9Hz), 6.90 (1H, dd, J=2, 8Hz), 7.11 (1H, d, J=2Hz), 7.37 (1H, d, J=8Hz), 7.64 (1H, dd, J=2, 9Hz), 8.09 (1H, d, J=2Hz), 8.65 (1H, d, J=7Hz), 9.11 (1H, t, J=6Hz)

Example 106

(1) (1*S*,3*R*)-1-Acetoxy-3-(*tert*-butyldimethylsilyloxy)cyclopentane (361 mg) was prepared from (1*R*,4*S*)-1-acetoxy-4-(*tert*-butyldimethylsilyloxy)-3-cyclopentene (474 mg) in a similar manner to Example 29-(3).
NMR ($CDCl_3$, δ): 0.04 (6H, s), 0.88 (9H, s), 1.55-1.93 (5H, m), 2.02 (3H, s), 2.23 (1H, m), 4.20 (1H, m), 5.03 (1H, m)

(2) To a solution of (1*S*,3*R*)-1-acetoxy-3-(*tert*-butyldimethylsilyloxy)-cyclopentane (361 mg) in ethanol (5 ml) was added 1*N* sodium hydroxide (2 ml) and the mixture was stirred at 25°C for 1 hour. The resulting mixture was evaporated *in vacuo*, diluted with ethyl acetate and washed with water and brine successively. The organic layer was dried over sodium sulfate and evaporated *in vacuo* to give (1*S*,3*R*)-3-(*tert*-butyldimethylsilyloxy)cyclopentane-1-ol (252 mg) as an oil.
NMR ($CDCl_3$, δ): 0.08 (6H, s), 0.88 (9H, s), 1.55-1.98 (6H, m), 3.06 (1H, d, J=9Hz), 4.24 (1H, m), 4.39 (1H, m)

(3)(1*S*,3*R*)-1-(*p*-Toluenesulfonyloxy)-3-(*tert*-butyldimethylsilyloxy)-cyclopentane (390 mg) was prepared from (1*S*,3*R*)-3-(*tert*-butyldimethyl-silyloxy)cyclopentane-1-ol (244 mg) and *p*-toluenesulfonyl chloride (258 mg) in a similar manner to Example 34-(1).
NMR ($CDCl_3$, δ): 0.01 (6H, s), 0.85 (9H, s), 1.64-1.87 (4H m), 1.97 (1H, m), 2.12 (1H, m), 2.45 (3H, s), 4.12 (1H, m), 4.86 (1H, m), 7.33 (2H, d, J=8Hz), 7.79 (2H, d, J=8Hz)

(4) (1*R*,3*R*)-1-Azido-3-(*tert*-butyldimethylsilyloxy)cyclopentane (168 mg) was prepared from (1*S*,3*R*)-1-(*p*-toluenesulfonyloxy)-3-(*tert*-butyldimethylsilyloxy)-cyclopentane (390 mg) and sodium azide (205 mg) in a similar manner to Example 34-(2).
NMR ($CDCl_3$, δ): 0.04 (6H, s), 0.87 (9H, s), 1.52-1.67 (3H, m), 1.76-2.00 (3H, m), 2.12 (1H, m), 4.08 (1H, m), 4.36 (1H, m)

(5) (1*R*,3*R*)-1-Amino-3-(*tert*-butyldimethylsilyloxy)cyclopentane (137 mg) was prepared from (1*R*,3*R*)-1-azido-3-(*tert*-butyldimethylsilyloxy)-cyclopentane (168 mg) in a similar manner to Example 29-(3).
NMR ($CDCl_3$, δ): 0.03 (6H, s), 0.88 (9H, s), 1.18-1.60 (3H, m), 1.84 (1H, m), 1.92-2.12 (2H, m), 3.56 (1H, m), 4.37 (1H, m)

(6) 2-[(1*R*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)cyclopentylamino]-*N*-(3-chloro-4-methoxybenzyl)-5-cyanobenzamide (76 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-5-cyano-2-fluorobenzamide (87 mg) and (1*R*,3*R*)-1-amino-3-(*tert*-butyldimethylsilyloxy)cyclopentane (65 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 0.04 (6H, s), 0.86 (9H, s), 1.39 (1H, m), 1.54 (1H, m),

1.65 (1H, m), 1.86-2.05 (2H, m), 2.22 (1H, m), 3.83 (3H, s), 4.02 (1H, m), 4.34 (2H, d, J=6Hz), 4.37 (1H, m), 6.78 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.25 (1H, dd, J=2, 9Hz), 7.37 (1H, d, J=2Hz) 7.63 (1H, dd, J=2,9Hz), 8.06 (1H, d, J=2Hz), 8.68 (1H, d, J=6Hz), 9.06 (1H, t, J=6Hz)

(7) *N*-(3-Chloro-4-methoxybenzyl)-5-cyano-2-[(1*R*,3*R*)-3-hydroxycyclo-pentylamino]benzamide (37 mg) was prepared from 2-[(1*R*,3*R*)-3-(*tert*-butyldimethylsilyloxy)cyclopentylamino]-N-(3-chloro-4-methoxybenzyl)-5-cyanobenzamide (73 mg) in a similar manner to Example 44-(4).

NMR (DMSO-d_6, δ): 1.34 (1H, m), 1.46-1.52 (2H, m), 1.88 (1H, m), 2.00 (1H, m), 2.21 (1H, m), 3.83 (3H, s), 4.01 (1H, m), 4.22 (1H, m), 4.34 (2H, d, J=6Hz), 4.63 (1H, d, J=4Hz), 6.79 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.25 (1H, dd, J=2, 9Hz), 7.37 (1H, d, J=2Hz), 7.63 (1H, dd, J=2, 9Hz), 8.06 (1H, d, J=2Hz), 8.67 (1H, d, J=6Hz), 9.04 (1H, t, J=6Hz)

Example 107

(1) 2-[(1*R*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-cyclopentylamino]-*N*-(4-chloro-3-methoxybenzyl)-5-cyanobenzamide (112 mg) was prepared from *N*-(4-chloro-3-methoxybenzyl)-5-cyano-2-fluorobenzamide (87 mg) and (1*R*,3*R*)-1-amino-3-(*t*-butyldimethylsilyloxy)cyclopentane (65 mg) in a similar manner to Example 12-(2).

NMR (DMSO-d_6, δ): 0.04 (6H, s), 0.86 (9H, s), 1.39 (1H, m), 1.54 (1H, m), 1.64 (1H, m), 1.86-2.05 (2H, m), 2.23 (1H, m), 3.84 (3H, s), 4.02 (1H, m), 4.37 (1H, m), 4.39 (2H, d, J=6Hz), 6.78 (1H, d, J=9Hz), 6.90 (1H, dd, J=2, 8Hz), 7.11 (1H, d, J=2Hz), 7.37 (1H, d, J=8Hz), 7.64 (1H, dd, J=2, 9Hz), 8.08 (1H, d, J=2Hz), 8.67 (1H, d, J=7Hz), 9.10 (1H, t, J=6Hz)

(2) *N*-(4-Chloro-3-methoxybenzyl)-5-cyano-2-[(1*R*,3*R*)-3-hydroxycyclo-pentylamino]benzamide (54 mg) was prepared from 2-[(1*R*,3*R*)-3-(*tert*-butyldimethylsilyloxy)cyclopentylamino]-*N*-(4-chloro-3-methoxybenzyl)-5-cyanobenzamide (108 mg) in a similar manner to Example 44-(4).

NMR (DMSO-d_6, δ): 1.34 (1H, m), 1.46-1.51 (2H, m), 1.87 (1H, m), 2.01 (1H, m), 2.21 (1H, m), 3.84 (3H, s), 4.02 (1H, m), 4.22 (1H, m), 4.40 (2H, d, J=6Hz), 4.64 (1H, d, J=4Hz), 6.79 (1H, d, J=9Hz), 6.89 (1H, dd, J=2, 8Hz), 7.11 (1H, d, J=2Hz), 7.37 (1H, d, J=8Hz), 7.63 (1H, dd, J=2, 9Hz),

8.07 (1H, d, J=2Hz), 8.66 (1H, d, J=7Hz), 9.09 (1H, t, J=6Hz)

Example 108

N-(3-Chloro-4-methoxybenzyl)-2-[(*S*)-(2-hydroxy-1-methylethyl)-amino]-5-(trifluoromethyl)benzamide (109 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-2-fluoro-5-(trifluoromethyl)benzamide (120 mg) and (*S*)-2-amino-1-propanol (37 mg) in a similar manner to Example 12-(2) as an amorphous powder.

NMR ($CDCl_3$, δ): 1.27 (3H, d, J=5Hz), 1.80-1.89 (1H, m), 3.58-3.82 (3H, m), 3.91 (3H, s), 4.50 (2H, d, J=5Hz), 6.30-6.39 (1H, m), 6.83 (1H, d, J=8Hz), 6.91 (1H, d, J=8Hz), 7.21 (1H, dd, J=8, 2Hz), 7.36 (1H, d, J=2Hz), 7.48 (1H, d, J=8Hz), 7.53 (1H, s), 8.00 (1H, d, J=8Hz)

Example 109

(1) *N*-(4-Chloro-3-methoxybenzyl)-2-fluoro-5-(trifluoromethyl)-benzamide (1.68 g) was prepared from 2-fluoro-5-(trifluoromethyl)benzoic acid (1.2 g) and 4-chloro-3-methoxybenzylamine (1.1 g) in a similar manner to Example 1-(3) as a white powder.

NMR ($CDCl_3$, δ): 3.09 (3H, s), 4.65 (2H, d, J=5Hz), 6.89 (1H, dd, J=8, 2Hz), 7.01 (1H, br), 7.26 (1H, t, J=8Hz), 7.34 (1H, d, J=8Hz), 7.70-7.80 (1H, m), 8.44 (1H, dd, J=8, 2Hz)

(2) *N*-(4-Chloro-3-methoxybenzyl)-2-[(*S*)-(2-hydroxy-1-methylethyl)-amino]-5-(trifluoromethyl)benzamide (97 mg) was prepared from *N*-(4-chloro-3-methoxybenzyl)-2-fluoro-5-(trifluoromethyl)benzamide (120 mg) and (*S*)-2-amino-1-propanol (37 mg) in a similar manner to Example 12-(2) as an amorphous powder.

NMR ($CDCl_3$, δ): 1.26 (3H d, J=5Hz), 1.86 (1H, br), 3.59-3.84 (3H, m), 3.91 (3H, s), 4.56 (2H, d, J=5Hz), 6.41 (1H, br), 6.84 (1H, d, J=8Hz), 6.89 (1H, dd, J=8, 2Hz), 6.92 (1H, s), 7.34 (1H, d, J=8Hz), 7.50 (1H, d, J=8Hz), 7.55 (1H, s), 8.00 (1H, d, J=8Hz)

Example 110

N-(3-Cyano-4-methoxybenzyl)-2-[(*R*)-(2-hydroxy-1-methylethyl)-amino]-5-(trifluoromethyl)benzamide (75 mg) was prepared from *N*-(3-cyano-4-methoxybenzyl)-2-fluoro-5-(trifluoromethyl)benzamide (120

mg) and (*R*)-2-amino-1-propanol (38 mg) in a similar manner to Example 12-(2) as an amorphous powder.
NMR ($CDCl_3$, δ): 1.28 (3H, d, J=5Hz), 1.86 (1H, t, J=3Hz), 3.59-3.82 (3H, m), 3.94 (3H, s), 4.55 (2H, d, J=5Hz), 6.46 (1H, br), 6.84 (1H, d, J=8Hz), 6.96 (1H, dd, J=8, 2Hz), 7.46-7.58 (4H, m), 8.01 (1H, d, J=8Hz)

Example 111

N-(3-Cyano-4-methoxybenzyl)-2-[(*S*)-(2-hydroxy-1-methylethyl)-amino]-5-(trifluoromethyl)benzamide (97 mg) was prepared from *N*-(3-cyano-4-methoxybenzyl)-2-fluoro-5-(trifluoromethyl)benzamide (120 mg) and (*S*)-2-amino-1-propanol (38 mg) in a similar manner to Example 12-(2) as an amorphous powder.
NMR ($CDCl_3$, δ): 1.27 (3H, d, J=5Hz), 1.90 (1H, t, J=5Hz), 3.59-3.85 (3H, m), 3.93 (3H, s), 4.54 (2H, d, J=5Hz), 6.59 (1H, br), 6.84 (1H, d, J=8Hz), 6.96 (1H, d, J=8Hz), 7.46-7.56 (4H, m), 8.00 (1H, d, J=8Hz)

Example 112

(1) *N*-(3-Chloro-4-methoxybenzyl)-2-(*trans*-4-hydroxycyclohexyl-amino)-5-(trifluoromethyl)benzamide (187 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-2-fluoro-5-(trifluoromethyl)benzamide (208 mg) and *trans*-4-aminocyclohexanol (199 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 1.15-1.42 (4H, m), 1.75-1.86 (2H, m), 1.92-2.02 (2H, m), 3.30-3.53 (2H, m), 3.83 (3H, s), 4.35 (2H, d, J=6Hz), 4.59 (1H, d, J=5Hz), 6.88 (1H, d, J=9Hz), 7.11 (1H, d, J=8Hz), 7.25 (1H, dd, J=2, 8Hz), 7.36 (1H, d, J=2Hz), 7.52 (1H, dd, J=2, 9Hz), 7.93 (1H, d, J=2Hz), 8.42 (1H, d, J=8Hz), 9.11 (1H, t, J=6Hz)

(2) 2-(*cis*-4-Benzoyloxycyclohexylamino)-*N*-(3-chloro-4-methoxybenzyl)-5-(trifluoromethyl)benzamide (150 mg) was prepared from *N*-(3-chloro-4-methoxybenzyl)-2-(*trans*-4-hydroxycyclohexylamino)-5-trifluoromethylbenzamide (200 mg) and benzoic acid (64 mg) in a similar manner to Example 58-(3) as an oil.
NMR ($CDCl_3$, δ): 1.76-2.14 (8H, m), 3.54 (1H, br), 3.89 (3H, s), 4.54 (1H, d, J=5Hz), 5.25 (1H, br), 6.30-6.38 (1H, m), 6.76 (1H, d, J=8Hz), 6.90 (1H, d, J=8Hz), 7.23 (1H, dd, J=8, 2Hz), 7.38 (1H, d, J=2Hz), 7.42-7.60 (5H, m), 8.05-8.10 (2H, m), 8.26 (1H, d, J=8Hz)

(3) *N*-(3-Chloro-4-methoxybenzyl)-2-(*cis*-4-hydroxycyclohexylamino)-5-(trifluoromethyl)benzamide (102 mg) was prepared from 2-(*cis*-4-benzoyloxycyclohexylamino)-*N*-(3-chloro-4-methoxybenzyl)-5-(trifluoromethyl)benzamide (150 mg) in a similar manner to Example 58-(4) as an amorphous powder.
NMR ($CDCl_3$, δ): 1.66-1.92 (8H, m), 3.52 (1H, br), 3.82-3.94 (4H, m), 4.51 (2H, d, J=5Hz), 6.30 (1H, br), 6.71 (1H, d, J=8Hz), 6.92 (1H, d, J=8Hz), 7.22 (1H, dd, J=8, 2Hz), 7.36 (1H, s), 7.46 (1H, d, J=8Hz), 7.52 (1H, s), 8.24 (1H, d, J=8Hz)

Example 113

(1) *N*-(4-Chloro-3-methoxybenzyl)-2-(*trans*-4-hydroxycyclohexylamino)-5-trifluoromethylbenzamide (282 mg) was prepared from *N*-(4-chloro-3-methoxybenzyl)-2-fluoro-5-trifluoromethylbenzamide (261 mg) and *trans*-4-aminocyclohexanol (249 mg) in a similar manner to Example 12-(2).
NMR (DMSO-d_6, δ): 1.13-1.38 (4H, m), 1.75-1.85 (2H, m), 1.92-2.00 (2H, m), 3.28-3.5 (2H, m), 3.84 (3H, s), 4.41 (2H, d, J=6Hz), 4.60 (1H, d, J=4Hz), 6.85-6.92 (2H, m), 7.11 (1H, d, J=2Hz), 7.37 (1H, d, J=9Hz), 7.53 (1H, dd, J=2, 9Hz), 7.96 (1H, d, J=2Hz), 8.39 (1H, d, J=8Hz), 9.15 (1H, t, J=6Hz)

(2) 2-(*cis*-4-Benzoyloxycyclohexylamino)-*N*-(4-chloro-3-methoxybenzyl)-5-(trifluoromethyl)benzamide (130 mg) was prepared from *N*-(4-chloro-3-methoxybenzyl)-2-(*trans*-4-hydroxycyclohexylamino)-5-(trifluoromethyl)benzamide (200 mg) and benzoic acid (64 mg) in a similar manner to Example 58-(3) as an oil.
NMR ($CDCl_3$, δ): 1.74-2.15 (8H, m), 3.54 (1H, br), 3.90 (3H, s), 4.59 (2H, d, J=5Hz), 5.23 (1H, br), 6.40 (1H, br), 6.26 (1H, d, J=8Hz), 6.85-6.95 (2H, m), 7.34 (1H, d, J=8Hz), 7.40-7.52 (3H, m), 7.52-7.61 (2H, m), 8.03-8.09 (2H, m), 8.25 (1H, d, J=8Hz)

(3) *N*-(4-Chloro-3-methoxybenzyl)-2-(*cis*-4-hydroxycyclohexylamino)-5-(trifluoromethyl)benzamide (97 mg) was prepared from 2-(*cis*-4-benzoyloxycyclohexylamino)-*N*-(4-chloro-3-methoxybenzyl)-5-(trifluoromethyl)benzamide (130 mg) in a similar manner to Example

58-(4) as an amorphous powder.
NMR ($CDCl_3$, δ): 1.65-1.92 (8H, m), 3.52 (1H, br), 3.82-3.94 (4H, m), 4.56 (2H, d, J=5Hz), 6.36 (1H, br), 6.73 (1H, d, J=8Hz), 6.94 (1H, s), 7.34 (1H, d, J=8Hz), 7.46 (1H, d, J=8Hz), 7.54 (1H, s), 8.23 (1H, br)

Example 114

(1) *N*-(3-Cyano-4-methoxybenzyl)-2-(*trans*-4-hydroxycyclohexylamino)-5-(trifluoromethyl)benzamide (257 mg) was prepared from *N*-(3-cyano-4-methoxybenzyl)-2-fluoro-5-(trifluoromethyl)benzamide (250 mg) and *trans*-4-aminocyclohexanol (123 mg) in a similar manner to Example 12-(2) as a powder.
NMR (DMSO-d_6, δ): 1.14-1.40 (4H, m), 1.76-1.86 (2H, m), 1.90-2.11 (2H, m), 3.22-3.63 (2H, m), 3.89 (3H, s), 4.37 (2H, d, J=5Hz), 4.64 (1H, d, J=4Hz), 6.88 (1H, d, J=8Hz), 7.23 (1H, d, J=8Hz), 7.53 (1H, dd, J=8, 2Hz), 7.56-7.77 (2H, m), 7.94 (1H, s), 8.39 (1H, d, J=8Hz), 9.11 (1H, t, J=5Hz)

(2) 2-(*cis*-4-Benzoyloxycyclohexylamino)-N-(3-cyano-4-methoxybenzyl)-5-(trifluoromethyl)benzamide (130 mg) was prepared from *N*-(3-cyano-4-methoxybenzyl)-2-(*trans*-4-hydroxycyclohexylamino)-5-(trifluoromethyl)benzamide (190 mg) and benzoic acid (62 mg) in a similar manner to Example 58-(3) as an oil.
NMR ($CDCl_3$, δ): 1.73-2.26 (8H, m), 3.53 (1H, br), 3.93 (3H, s), 4.56 (2H, d, J=5Hz), 5.24 (1H, br), 6.38-6.51 (1H, m), 6.76 (1H, d, J=8Hz), 6.95 (1H, d, J=8Hz), 7.41-7.65 (7H, m), 8.04-8.14 (2H, m), 8.26 (1H, d, J=8Hz)

(3) *N*-(3-Cyano-4-methoxybenzyl)-2-(*cis*-4-hydroxycyclohexylamino)-5-(trifluoromethyl)benzamide (74 mg) was prepared from 2-(*cis*-4-benzoyloxycyclohexylamino)-*N*-(3-cyano-4-methoxybenzyl)-5-(trifluoromethyl)benzamide (130 mg) in a similar manner to Example 58-(4) as a powder.
NMR ($CDCl_3$, δ): 1.46 (1H, d, J=5Hz), 1.65-1.91 (8H, m), 3.48-3.59 (1H, m), 3.88 (1H, br), 3.93 (3H, s), 4.54 (2H, d, J=5Hz), 6.42 (1H, br), 6.73 (1H, d, J=8Hz), 6.96 (1H, d, J=8Hz), 7.46 (1H, d, J=8Hz), 7.51-7.58 (3H, m), 8.21 (1H, d, J=8Hz)

Example 115

(1) 2-(*trans*-4-Aminocyclohexylamino)-*N*-(3-cyano-4-methoxybenzyl)-

5-(trifluoromethyl)benzamide (164 mg) was prepared from *N*-(3-cyano-4-methoxybenzyl)-2-fluoro-5-(trifluoromethyl)benzamide (200 mg) and *trans*-1,4-diaminocyclohexane (97 mg) in a similar manner to Example 12-(2) as a powder.

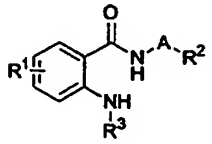
NMR ($CDCl_3$, δ): 1.11-1.30 (4H, m), 1.70-1.85 (2H, m), 1.78-2.03 (2H, m), 2.61 (1H, br), 3.89 (3H, s), 4.37 (2H, d, J=5Hz), 6.86 (1H, d, J=8Hz), 7.23 (1H, d, J=8Hz), 7.52 (1H, d, J=8Hz), 7.59-7.68 (2H, m), 7.94 (1H, s), 8.36 (1H, d, J=8Hz), 9.12 (1H, t, J=5Hz)

(2) 2-[*trans*-4-(Formamido)cyclohexylamino]-*N*-(3-cyano-4-methoxybenzyl)-5-(trifluoromethyl)benzamide (83 mg) was prepared from 2-(*trans*-4-aminocyclohexylamino)-*N*-(3-cyano-4-methoxybenzyl)-5-(trifluoromethyl)benzamide (161 mg) in a similar manner to Example 70-(2) as a powder.

NMR ($CDCl_3$, δ): 1.25-1.50 (4H, m), 2.01-2.23 (4H, m), 3.33 (1H, br), 3.83-3.99 (4H, m), 4.53 (2H, d, J=5Hz), 5.38 (1H, brd, J=7.5Hz), 6.51 (1H, br), 6.70 (1H, d, J=8Hz), 6.96 (1H, d, J=8Hz), 7.44-7.58 (4H, m), 8.06 (1H, d, J=8Hz), 8.14 (1H, s)

CLAIMS

1. A compound of the formula [I] :



[I]

wherein

R^1 is nitro group, amino group, cyano group, an acyl group, a halo(lower)alkyl group, sulfamoyl group, a carbamoyl group optionally substituted with lower alkyl, a halogen atom, a lower alkenyl group optionally substituted with protected carboxy, a lower alkanesulfonyl group, a saturated heterocyclic sulfonyl group optionally substituted with protected carboxy or an unsaturated heterocyclic group,

R^2 is hydrogen atom, hydroxy group, a lower alkoxy group, a lower alkyl group, a cycloalkyl group, an optionally substituted aryl group or a heterocyclic group optionally substituted with lower alkyl,

A is a lower alkylene group and

R^3 is an optionally substituted heterocyclic group or a group of the formula : $-CR^4R^5R^6$, in which

R^4 and R^5 are each independently a carbamoyl group or a lower alkyl group optionally substituted with one or more substituent(s) selected from the group consisting of hydroxy group and an amino group optionally substituted with acyl, protected carboxy, carbamoyl or lower alkylcarbamoyl, or

R^4 and R^5 together with the carbon atom to which R^4 and R^5 are attached may form an optionally substituted carbocyclic group, and

R^6 is hydrogen atom or a lower alkyl group,

and a pro-drug thereof, and a salt thereof.

2. A compound of Claim 1, wherein

R^1 is nitro group, amino group, cyano group, a halo(lower)alkyl group or a halogen atom,

R^2 is hydrogen atom, a lower alkyl group, a cycloalkyl group, an aryl group optionally substituted with one or more substituent(s) selected from the group consisting of a halogen atom, cyano group, a lower alkyl group and a lower alkoxy group, or pyridyl group and

R^3 is a saturated 3 to 7-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) or 1 to 2 oxygen atom(s) optionally substituted with one or more substituent(s) selected from the group consisting of carbamoyl group, sulfamoyl group, a protected carboxy group and a lower alkyl group optionally substituted with hydroxy; or

a group of the formula : $-CR^4R^5R^6$, in which

R^4 and R^5 are each independently a carbamoyl group or a lower alkyl group optionally substituted with one or more substituent(s) selected from the group consisting of hydroxy group and an amino group optionally substituted with acyl, protected carboxy, carbamoyl or lower alkylcarbamoyl, or

R^4 and R^5 together with the carbon atom to which R^4 and R^5 are attached may form a carbocyclic group optionally substituted with one or more substituent(s) selected from the group consisting of a lower alkyl group, hydroxy group, a protected hydroxy group, a lower alkoxy group, an amino group optionally substituted with acyl, an ureido group optionally substituted with lower alkyl, a lower alkylenedioxy group optionally substituted with oxo and a cycloalkylidenedioxy group, and

R^6 is hydrogen atom or a lower alkyl group.

3. A compound of Claim 2, wherein

R^3 is a group of the formula : $-CR^4R^5R^6$ in which

R^4 and R^5 together with the carbon atom to which R^4 and R^5 are attached may form a carbocyclic group substituted

with one or more substituent(s) selected from the group consisting of a lower alkyl group, hydroxy group, a protected hydroxy group, a lower alkoxy group, an amino group optionally substituted with acyl, an ureido group optionally substituted with lower alkyl, a lower alkylenedioxy group optionally substituted with oxo, and a cycloalkylidenedioxy group, and

R^6 is hydrogen atom or a lower alkyl group.

4. A compound of Claim 2, wherein

R^2 is an aryl group substituted with one ore more substituent(s) selected from the group consisting of a halogen atom, cyano group, a lower alkyl group and a lower alkoxy group.

5. A compound of Claim 3, wherein

R^1 is cyano group or a halo(lower)alkyl group,

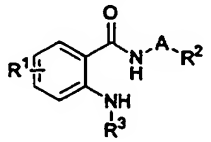
R^2 is a phenyl group substituted with one or two substituent(s) selected from the group consisting of a halogen atom, cyano group and a lower alkoxy group, and

R^3 is a group of the formula : $-CR^4R^5R^6$ in which

R^4 and R^5 together with the carbon atom to which R^4 and R^5 are attached may form a carbocyclic group substituted with one or two substituent(s) selected from the group consisting of hydroxy group, a lower alkoxy group and a lower alkanoylamino group, and

R^6 is hydrogen atom.

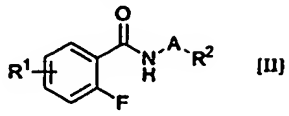
6. A process for preparing a compound of the formula [I] :



[I]

wherein R^1, R^2, R^3 and A are the same as those defined in Claim 1, and a pro-drug thereof, and a salt thereof, which comprises

a) reacting a compound of the formula [II] :

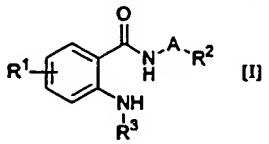


[II]

or its salt, with a compound of the formula [III]:

H_2N-R^3 [III]

or its salt, to give a compound of the formula [I]:



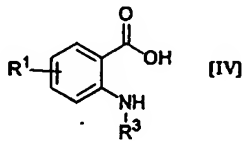
[I]

or its salt,

wherein R^1, R^2, R^3 and A are the same as those defined in the above,

or

b) reacting a compound of the formula [IV]:

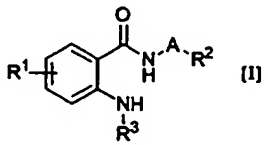


[IV]

or its reactive derivative at the carboxy group or a salt thereof, with a compound of the formula [V]:

H_2N-A-R^2 [V]

or its reactive derivative at the amino group or a salt thereof, to give a compound of the formula [I]:



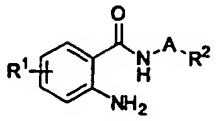
[I]

or its salt,

wherein R^1, R^2, R^3 and A are the same as those defined in the above,

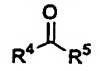
or

c) reacting a compound of the formula [VI]:



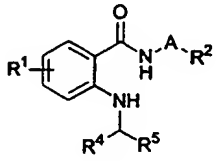
[VI]

or its salt, with a compound of the formula [VII]:



[VII]

or its salt, to give a compound of the formula [I-1]:



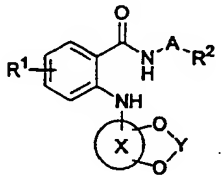
[I-1]

or its salt,

wherein R^1, R^2, R^4, R^5 and A are the same as those defined in the above,

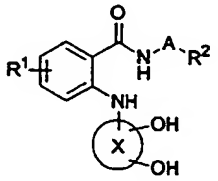
or

d) subjecting a compound of the formula [I-2]:



[I-2]

or its salt, to a hydrolysis reaction to give a compound of the formula [I-3]:



[I-3]

or its salt,

wherein a ring (X) is a carbocyclic group,

Y is cycloalkylidene, and

R^1, R^2 and A are the same as those defined in the above.

7. A pharmaceutical composition comprising a compound of Claim 1, as an active ingredient, in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

8. A compound of Claim 1 for use as a medicament.

9. Use of a compound of Claim 1 for the manufacture of a medicament for the treatment and/or prevention of angina, hypertension, pulmonary hypertension, congestive heart failure, glomerular diseases, renal tubulo-interstitial diseases, renal failure, atherosclerosis, conditions of reduced blood vessel patency, peripheral vascular disease, stroke, bronchitis, asthma, allergic rhinitis, urticaria, glaucoma, diseases characterized by disorders of gut motility, erectile dysfunction, female sexual dysfunction, impotence, diabetic complications, micturition disorder, or incontinence or storage of urine disorder.

10. A method for the treatment and/or prevention of angina, hypertension, pulmonary hypertension, congestive heart failure, glomerular diseases, renal tubulo-interstitial diseases, renal failure, atherosclerosis, conditions of reduced blood vessel patency, peripheral vascular disease, stroke, bronchitis, asthma, allergic rhinitis, urticaria, glaucoma, diseases characterized by disorders of gut motility, erectile dysfunction, female sexual dysfunction, impotence, diabetic complications, micturition disorder, or incontinence or storage of urine disorder, by administering an effective amount of a compound of Claim 1 to a patient suffering any of the diseases or disorders.

11. An article comprising a packaging material and a pharmaceutical composition containing a compound of Claim 1 contained within said packaging material, wherein said compound is therapeutically effective for the treatment and/or prevention of angina, hypertension, pulmonary hypertension, congestive heart failure, glomerular diseases, renal

tubulo-interstitial diseases, renal failure, atherosclerosis, conditions of reduced blood vessel patency, peripheral vascular disease, stroke, bronchitis, asthma, allergic rhinitis, urticaria, glaucoma, diseases characterized by disorders of gut motility, erectile dysfunction, female sexual dysfunction, impotence, diabetic complications, micturition disorder, or incontinence or storage of urine disorder, and wherein said packaging material comprises a label which indicates that said pharmaceutical composition can be used for the treatment and/or prevention of angina, hypertension, pulmonary hypertension, congestive heart failure, glomerular diseases, renal tubulo-interstitial diseases, renal failure, atherosclerosis, conditions of reduced blood vessel patency, peripheral vascular disease, stroke, bronchitis, asthma, allergic rhinitis, urticaria, glaucoma, diseases characterized by disorders of gut motility, erectile dysfunction, female sexual dysfunction, impotence, diabetic complications, micturition disorder, or incontinence or storage of urine disorder.

12. A commercial package comprising the pharmaceutical composition containing a compound of Claim 1 and a written matter associated therewith, wherein the written matter states that the pharmaceutical composition can or should be used for the treatment and/or prevention of angina, hypertension, pulmonary hypertension, congestive heart failure, glomerular diseases, renal tubulo-interstitial diseases, renal failure, atherosclerosis, conditions of reduced blood vessel patency, peripheral vascular disease, stroke, bronchitis, asthma, allergic rhinitis, urticaria, glaucoma, diseases characterized by disorders of gut motility, erectile dysfunction, female sexual dysfunction, impotence, diabetic complications, micturition disorder, or incontinence or storage of urine disorder.

INTERNATIONAL SEARCH REPORT

Inten d Application No
PCT/JP 00/07308

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C237/30 C07C237/32 C07C255/58 A61K31/166 A61K31/40
A61K31/277 A61K31/357 A61P9/10 C07C255/59 C07C271/20
C07D207/14 C07D317/72

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BEILSTEIN Data, EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 54284 A (FUJISAWA) 28 October 1999 (1999-10-28) page 20 -page 29; claims; examples	1-12
X	EP 0 686 625 A (EISAI) 13 December 1995 (1995-12-13) cited in the application page 3, line 1 - line 31; claims; examples 29-34,46,47,49,50,110-112,122,123,136,137, 142-144	1-12

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 January 2001	06/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Zervas, B

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. KOSARY ET AL.: "Synthesis and Biological Activity of 2,5-Diaminobenzoic Acids Stimulating the Biosynthesis of Prostaglandins" PHARMAZIE., vol. 37, no. 7, 1982, pages 484-486, XP002157673 BERLIN DD page 485, table 2, compound 3t; page 486, table 3, compound 1t	1-4,6-8

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern al Application No
PCT/JP 00/07308

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9954284 A	28-10-1999	AU 3170899 A	08-11-1999
EP 686625 A	13-12-1995	AU 694465 B	23-07-1998
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